

## PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR MODULATORS

### FIELD OF THE INVENTION

The present invention relates to compounds of peroxisome proliferator  
5 activated receptor (PPAR) agonists, more specifically compounds of PPAR gamma-delta  
dual agonists, which are useful for the treatment and/or prevention of disorders modulated  
by a PPAR agonist.

### BACKGROUND OF THE INVENTION

10 The peroxisome proliferator activated receptors (PPARs) are members of  
the nuclear receptor gene family that are activated by fatty acids and fatty acid  
metabolites. The PPARs belong to the subset of nuclear receptors that function as  
heterodimers with the 9-*cis* retinoic acid receptor (RXR). Three subtypes, which are  
designated as PPAR $\alpha$ , PPAR $\gamma$  and PPAR $\delta$  are found in species ranging from *Xenopus* to  
15 humans.

PPAR $\alpha$  is the main subtype in the liver and has facilitated analysis of the  
mechanism by which peroxisome proliferators exert their pleiotropic effects. PPAR $\alpha$  is  
activated by a number of medium and long-chain fatty acids, and it is involved in  
stimulating  $\beta$ -oxidation of fatty acids. PPAR $\alpha$  is also involved with the activity of  
20 fibrates and fatty acids in rodents and humans. Fibrates such as clofibrate,  
fenofibrate, bezafibrate, ciprofibrate, beclofibrate and etofibrate, as well as gemfibrozil,  
produce a substantial reduction in plasma triglycerides along with moderate reduction in  
low-density lipoprotein (LDL) cholesterol, and they are used particularly for the treatment  
of hypertriglyceridemia.

25 PPAR $\gamma$  is the main subtype in adipose tissue and involved in activating the  
program of adipocyte differentiation. PPAR $\gamma$  is not involved in stimulating peroxisome  
proliferation in the liver. There are two isomers of PPAR $\gamma$ : PPAR $\gamma$ 1 and PPAR $\gamma$ 2, which  
differ only in that PPAR $\gamma$ 2 contains an additional 28 amino acids present at the amino  
terminus. The DNA sequences for the PPAR $\gamma$  receptors are described in Elbrecht, et al.,  
30 BBRC 224;431-437 (1996). Although peroxisome proliferators, including the fibrates  
and fatty acids, activate the transcriptional activity of PPAR's, only prostaglandin J<sub>2</sub>

derivatives have been identified as natural ligands for PPAR $\gamma$ , which also binds the anti-diabetic agents thiazolidinediones with high affinity. The physiological functions of PPAR $\alpha$  and PPAR $\gamma$  in lipid and carbohydrate metabolism were uncovered once it was recognized that they were the receptors for the fibrate and glitazone drugs, respectively.

5 PPAR $\alpha$  and PPAR $\gamma$  receptors have been implicated in diabetes mellitus, cardiovascular disease, obesity, and gastrointestinal disease, such as inflammatory bowel disease and other inflammation related illnesses. Such inflammation related illnesses include, but are not limited to Alzheimer's disease, Crohn's disease, rheumatoid arthritis, psoriasis, and ischemia reprofusion injury.

10 By contrast, PPAR $\delta$  (also referred to as PPAR $\beta$  and NUC1) is not reported to be receptor for any known class of drug molecules, and its role in mammalian physiology has remained undefined. The human nuclear receptor gene PPAR $\delta$  (hPPAR $\delta$ ) has been cloned from a human osteosarcoma cell cDNA library and is fully described in A. Schmidt et al., *Molecular Endocrinology*, 6:1634-1641 (1992).

15 Diabetes is a disease in which a mammal's ability to regulate glucose levels in the blood is impaired because the mammal has a reduced ability to convert glucose to glycogen for storage in muscle and liver cells. In Type I diabetes, this reduced ability to store glucose is caused by reduced insulin production. "Type II Diabetes" or "non-insulin dependent diabetes mellitus" (NIDDM) is the form of diabetes, which is due  
20 to a profound resistance to insulin stimulating or regulatory effect on glucose and lipid metabolism in the main insulin-sensitive tissues, muscle, liver and adipose tissue. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. When these cells become  
25 desensitized to insulin, the body tries to compensate by producing abnormally high levels of insulin and hyperinsulemia results. Hyperinsulemia is associated with hypertension and elevated body weight. Since insulin is involved in promoting the cellular uptake of glucose, amino acids and triglycerides from the blood by insulin sensitive cells, insulin insensitivity can result in elevated levels of triglycerides and LDL (known as the "bad"  
30 cholesterol) which are risk factors in cardiovascular diseases. The constellation of

symptoms which includes hyperinsulemia combined with hypertension, elevated body weight, elevated triglycerides and elevated LDL is known as Syndrome X.

Hyperlipidemia is a condition which is characterized by an abnormal increase in serum lipids, such as cholesterol, triglycerides and phospholipids. These lipids do not circulate freely in solution in plasma, but are bound to proteins and transported as macromolecular complexes called lipoproteins. One form of hyperlipidemia is hypercholesterolemia, characterized by the existence of elevated LDL cholesterol levels. The initial treatment for hypercholesterolemia is often a diet low in fat and cholesterol coupled with appropriate physical exercise. Drug intervention is initiated if LDL-lowering goals are not met by diet and exercise alone. It is desirable to lower elevated levels of LDL cholesterol and increase levels of HDL cholesterol. Generally, it has been found that increased levels of HDL are associated with lower risk for coronary heart disease (CHD). See Gordon, et al., *Am. J. Med.*, 62, 707-714 (1977); Stampfer, et al., *N. England J. Med.*, 325, 373- 381 (1991); and Kannel, et al., *Ann. Internal Med.*, 90, 85-91 (1979). An example of an HDL raising agent is nicotinic acid, but the quantities needed to achieve HDL elevation are associated with undesirable effects, such as flushing.

There are several treatments currently available for treating diabetes mellitus but these treatments still remain unsatisfactory and have limitations. While physical exercise and reduction in dietary intake of calories will improve the diabetic condition, compliance with this approach can be poor because of sedentary lifestyles and excess food consumption, in particular high fat-containing food. Therefore, treatment with hypoglycemics, such as sulfonylureas (e.g., chlorpropamide, tolbutamide, tolazamide and acetohexamide) and biguanides (e.g. phenformin and metformin) are often necessary as the disease progresses. Sulfonylureas stimulate the  $\beta$  cells of the pancreas to secrete more insulin as the disease progresses. However, the response of the  $\beta$  cells eventually fails and treatment with insulin injections is necessary. In addition, both sulfonylurea treatment and insulin injection have the life threatening side effect of hypoglycemic coma, and thus patients using these treatments must carefully control dosage.

It has been well established that improved glycemic control in patients with diabetes (Type I and Type II) is accompanied by decreased microvascular

complications (DCCT and UKPDS). Due to difficulty in maintaining adequate glycemic control over time in patients with Type II diabetes, the use of insulin sensitizers in the therapy of Type II diabetes is growing. There is also a growing body of evidence that PPAR $\gamma$  agonist, insulin sensitizer, may have benefits in the treatment of Type II diabetes beyond their effects in improving glycemic control.

In the last decade a class of compounds known as thiazolidinediones (TZD) (e.g. U.S. Pat. Nos. 5,089,514; 4,342,771; 4,367,234; 4,340,605; and 5,306,726) have emerged as effective antidiabetic agents that have been shown to increase the sensitivity of insulin sensitive tissues, such as skeletal muscle, liver and adipose, to insulin. Increasing insulin sensitivity rather than the amount of insulin in the blood reduces the likelihood of hypoglycemic coma. Although thiazolidinediones have been shown to increase insulin sensitivity by binding to PPAR $\gamma$  receptors, this treatment also produces unwanted side effects such as weight gain and edema and, for troglitazone, liver toxicity. Recently, the compounds that are not TZDs have also been reported as PPAR modulators.

Adams et al. (WO 97/28115, WO 97/28135 and US Patent No. 5,895,051) discloses acetylphenols, which are useful as antiobesity and antidiabetic compounds.

Leibowitz et al. (WO 97/28149) discloses compounds which are PPAR $\delta$  agonists and useful for treating cardiovascular diseases and related conditions.

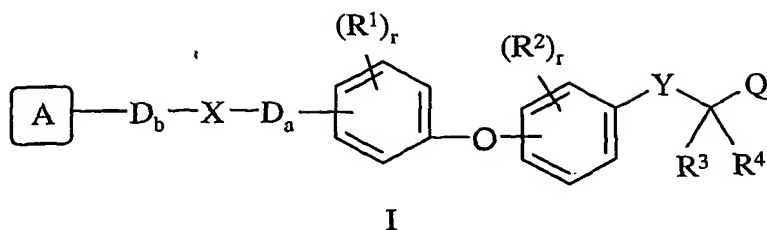
Brooks et al. (WO 02/100813) discloses compounds of PPAR modulators that are useful for treating type II diabetes and other PPAR-mediated diseases and conditions.

In view of the above, an objective of the present invention is to provide new pharmaceutical agents which modulate PPAR receptors to prevent, treat and/or alleviate these diseases or conditions while reducing and or eliminating one or more of the unwanted side effects associated with the current treatments.

#### SUMMARY OF THE INVENTION

The present invention relates to a compound of novel peroxisome proliferator activated receptor (PPAR) agonist having a structural formula I,





or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:



is:

- a) aryl,
- b) a 5- to 10-membered heteroaryl wherein the heteroaryl containing at least one heteroatom selected from N, O or S,
- c) C<sub>3</sub>-C<sub>8</sub> cycloalkyl,
- d) aliphatic group, or
- e) heterocyclyl,

wherein aryl, heteroaryl, cycloalkyl, heterocyclyl and aliphatic group being optionally substituted with one or more groups independently selected from R<sup>8</sup>;

D<sub>a</sub> and D<sub>b</sub> are each independently:

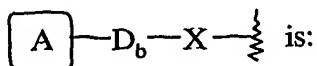
a bond or

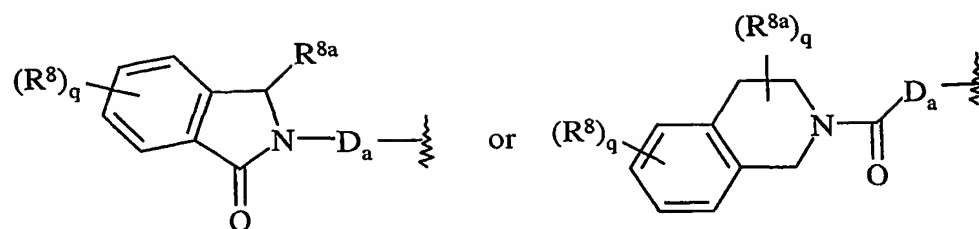
-[C(R<sup>c</sup>)(R<sup>d</sup>)]<sub>n</sub>, wherein R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or aryl;

Q is: -C(O)OR<sup>5</sup> or R<sup>5A</sup>;

X is: NR<sup>6</sup>C[O]<sub>p</sub>,  
NR<sup>6</sup>S(O)<sub>2</sub>,  
C[O]<sub>p</sub>NR<sup>6</sup>,  
S(O)<sub>2</sub>NR<sup>6</sup> or  
NR<sup>7</sup>;

Y is: a bond, CH<sub>2</sub>, S or O;





n and r are each independently: 1, 2, 3 or 4;

q is: 1, 2, 3, 4 or 5;

p is: 1 or 2;

5

R<sup>1</sup> and R<sup>2</sup> are each independently: hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, halo or haloalkyl;

R<sup>3</sup> and R<sup>4</sup> are each independently:

hydrogen,

10

halo,

C<sub>1</sub>-C<sub>6</sub> alkyl,

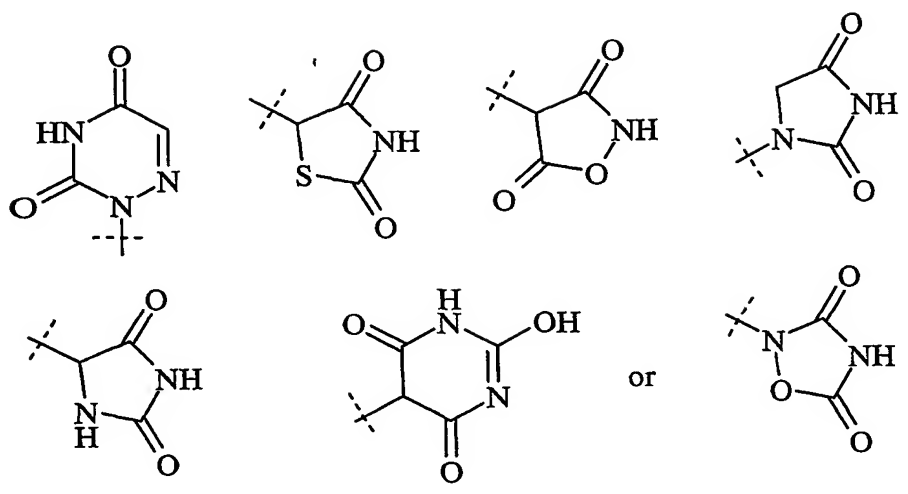
C<sub>1</sub>-C<sub>6</sub> alkoxy or

aryloxy;

15 R<sup>3</sup> and R<sup>4</sup> are together a 3- to 6- membered carbocyclyl or heterocyclyl;

R<sup>5</sup> is: hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or aminoalkyl;

R<sup>5A</sup> is: carboxamide, sulfonamide, acylsulfonamide, tetrazole,



$R^6$  is each independently:

hydrogen,

5  $C_1$ - $C_{12}$  alkyl,

arylalkyl,

$C_3$ - $C_8$  cycloalkyl, or

$(CH_2)_nC(O)aryl$ ,

10 wherein alkyl, arylalkyl and cycloalkyl group being optionally substituted with one or more groups independently selected from  $R^8$ ;

$R^7$  is: hydrogen,

acyl, or

sulfonyl;

15

$R^8$  and  $R^{8a}$  are each independently:

hydrogen,

$C_1$ - $C_6$  alkyl,

$C_1$ - $C_6$  alkoxy,

20

nitro,

cyano,

halo,

haloalkyl,  
haloalkyloxy,  
aryl,  
heteroaryl,  
5 benzyl,  
aryloxy,  
SR<sup>9</sup>,  
S[O]<sub>p</sub>R<sup>9</sup> or  
C[O]<sub>p</sub>R<sup>9</sup>; and

10 R<sup>9</sup> is: hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, or C<sub>3</sub>-C<sub>8</sub> cycloalkyl.

The compounds of the present invention are useful in the treatment and/or prevention of diseases or condition relates to hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, 15 anorexia bulimia, anorexia nervosa, cardiovascular disease and other diseases where insulin resistance is a component.

In one embodiment, the present invention also relates to a pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate or hydrate thereof and a pharmaceutically acceptable carrier. 20 Within the scope of this invention also include a pharmaceutical composition containing additional therapeutic agent as well as a compound of the present invention, or a pharmaceutically acceptable salt, solvate or hydrate thereof and a pharmaceutically acceptable carrier.

25 In another embodiment, the present invention relates to a method of modulating a PPAR by contacting the receptor with a compound of the present invention, and a pharmaceutically acceptable salt, solvate or hydrate thereof.

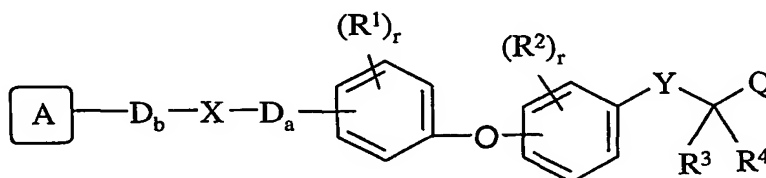
#### DETAILED DESCRIPTION OF THE INVENTION

30 The compounds of the present invention are directed to peroxisome proliferator activated receptor (PPAR) agonists, more specifically compounds of

PPAR $\gamma/\delta$  dual agonists, which are useful for the treatment and/or prevention of disorders modulated by a PPAR, such as Type II diabetes, hyperglycemia, dyslipidemia, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia

5 bulimia, anorexia nervosa, cardiovascular disease and other related diseases.

An embodiment of the present invention is a compound of novel peroxisome proliferator activated receptor (PPAR) agonists having a structural formula I,



I

10 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:



- is:
- a) aryl,
  - b) a 5- to 10-membered heteroaryl wherein the heteroaryl containing at least one heteroatom selected from N, O or S,
  - c) C<sub>3</sub>-C<sub>8</sub> cycloalkyl,
  - 15 d) aliphatic group, or
  - e) heterocyclyl,

wherein aryl, heteroaryl, cycloalkyl, heterocyclyl and aliphatic group being optionally substituted with one or more groups independently selected from R<sup>8</sup>;

20 D<sub>a</sub> and D<sub>b</sub> are each independently:

a bond or

-[C(R<sup>c</sup>)(R<sup>d</sup>)]<sub>n</sub>, wherein R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or aryl;

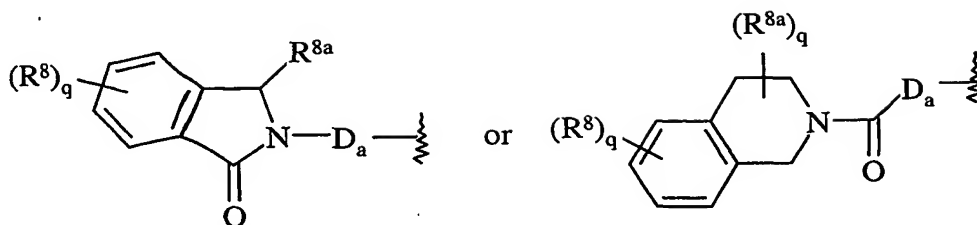
25 Q is: -C(O)OR<sup>5</sup> or R<sup>5A</sup>;

X is: NR<sup>6</sup>C[O]<sub>p</sub>,  
NR<sup>6</sup>S(O)<sub>2</sub>,

$C[O]_p, NR^6$ ,  
 $S(O)_2NR^6$  or  
 $NR^7$ ;

5 Y is: a bond,  $CH_2$ , S or O;

$\boxed{A}-D_b-X-\text{wavy line}$  is:



n and r are each independently: 1, 2, 3 or 4;

q is: 1, 2, 3, 4 or 5;

10 p is: 1 or 2;

$R^1$  and  $R^2$  are each independently: hydrogen,  $C_1-C_6$  alkyl, halo or haloalkyl;

$R^3$  and  $R^4$  are each independently:

15 hydrogen,  
 halo,  
 $C_1-C_6$  alkyl,  
 $C_1-C_6$  alkoxy or  
 aryloxy;

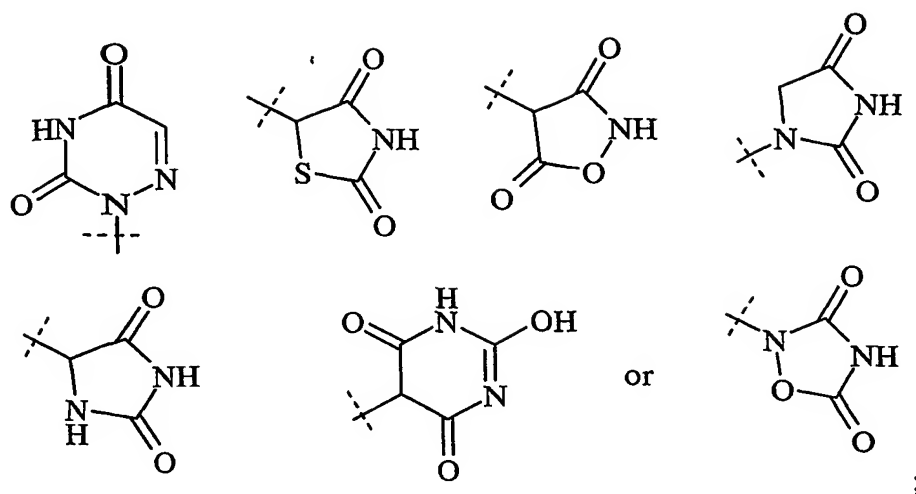
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$R^3$  and  $R^4$  are together a 3- to 6- membered carbocyclyl or heterocyclyl;

$R^5$  is: hydrogen,  $C_1-C_6$  alkyl or aminoalkyl;

25

$R^{5A}$  is: carboxamide, sulfonamide, acylsulfonamide, tetrazole,



$R^6$  is each independently:

hydrogen,

5

$C_1$ - $C_{12}$  alkyl,

arylalkyl,

$C_3$ - $C_8$  cycloalkyl, or

$(CH_2)_n C(O) aryl$ ,

wherein alkyl, arylalkyl and cycloalkyl group being optionally substituted with

10

one or more groups independently selected from  $R^8$ ;

$R^7$  is: hydrogen,

acyl, or

sulfonyl;

15

$R^8$  and  $R^{8a}$  are each independently:

hydrogen,

$C_1$ - $C_6$  alkyl,

$C_1$ - $C_6$  alkoxy,

20

nitro,

cyano,

halo,

haloalkyl,

haloalkyloxy,

aryl,

heteroaryl,

benzyl,

5 aryloxy,

$SR^9$ ,

$S[O]_pR^9$  or

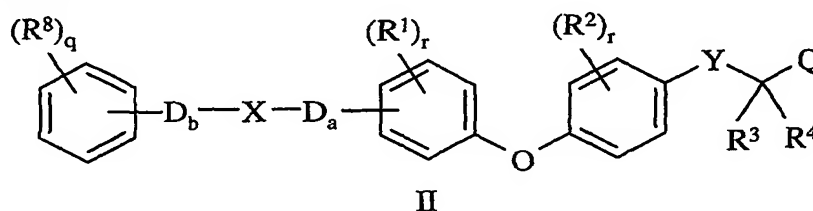
$C[O]_pR^9$ ; and

10  $R^9$  is: hydrogen,  $C_1$ - $C_6$  alkyl, or  $C_3$ - $C_8$  cycloalkyl.

The compound as recited above, wherein aryl or heteroaryl are selected from the group consisting of phenyl, naphthyl, indolyl, isoindolyl, benzoimidazolyl, quinolinyl, isoquinolinyl, pyridyl, benzothiophenyl and benzofuranyl.

A preferred embodiment of the present invention is a compound having a

15 structural formula II,



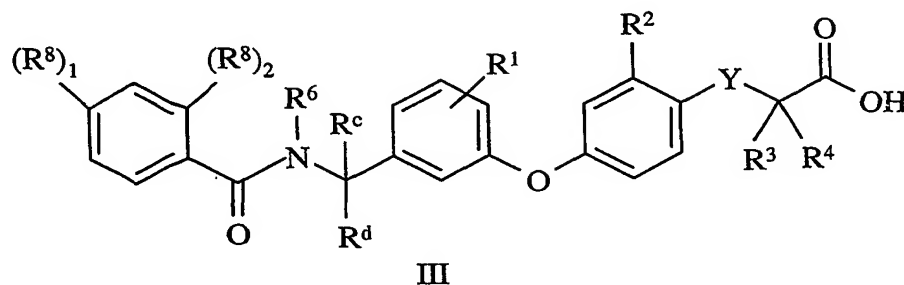
or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

20 q is 1, 2, 3, 4, or 5.

The compound as recited above in formula II, wherein  $R^8$  is disubstituted in 2 and 4 positions, or trisubstituted in 2, 4, and 6 positions of phenyl ring relative to  $-D_b-$ .

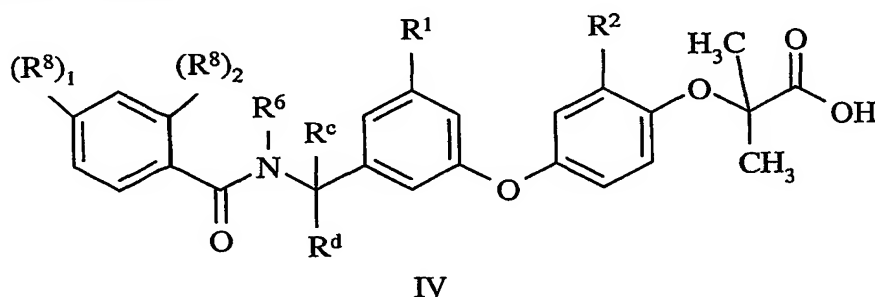


Another preferred embodiment of the present invention is a compound having a structural formula III,



- 5 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:  
 Y is: O or CH<sub>2</sub>;  
 R<sup>1</sup> is: hydrogen, halo or C<sub>1</sub>-C<sub>4</sub> alkyl;  
 R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup>, R<sup>6</sup>, R<sup>c</sup> and R<sup>d</sup> are each independently: hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl;  
 (R<sup>8</sup>)<sub>1</sub> and (R<sup>8</sup>)<sub>2</sub> are each independently:  
 10 hydrogen, halo, haloalkyl or haloalkyloxy, cyano, nitro, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy or SR<sup>9</sup>;  
 R<sup>6</sup> is: hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl; and  
 R<sup>9</sup> is: hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>3</sub>-C<sub>6</sub> cycloalkyl.

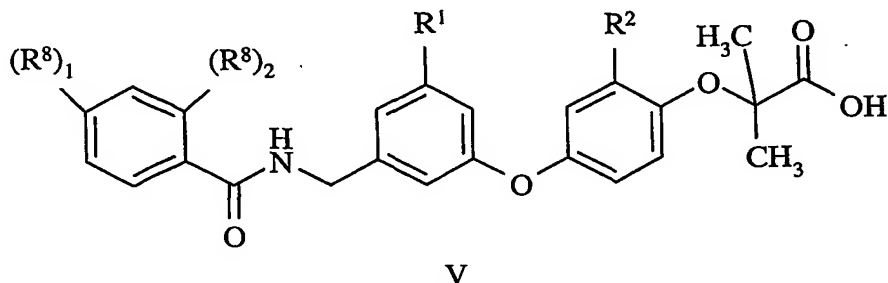
Yet another preferred embodiment of the present invention is the compound having a structural formula IV,



15

- or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:  
 R<sup>1</sup> and R<sup>2</sup> are each independently: hydrogen, halo or C<sub>1</sub>-C<sub>4</sub> alkyl;  
 R<sup>c</sup>, R<sup>d</sup> and R<sup>6</sup> are each independently: hydrogen or methyl; and  
 20 (R<sup>8</sup>)<sub>1</sub> and (R<sup>8</sup>)<sub>2</sub> are each independently:  
 hydrogen, F, Cl, Br, OMe, CF<sub>3</sub>, OCF<sub>3</sub>, SCH<sub>3</sub>, NO<sub>2</sub>, cyano, methyl, ethyl, isobutyl,  
 isopropyl or *tert*-butyl.

Yet another preferred embodiment of the present invention is the compound having a structural formula V,



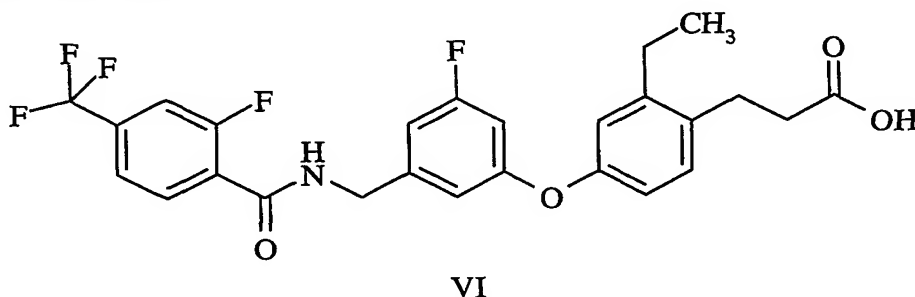
5 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$R^1$  and  $R^2$  are each independently: hydrogen, methyl, ethyl or fluoro; and

$(R^8)_1$  and  $(R^8)_2$  are each independently:

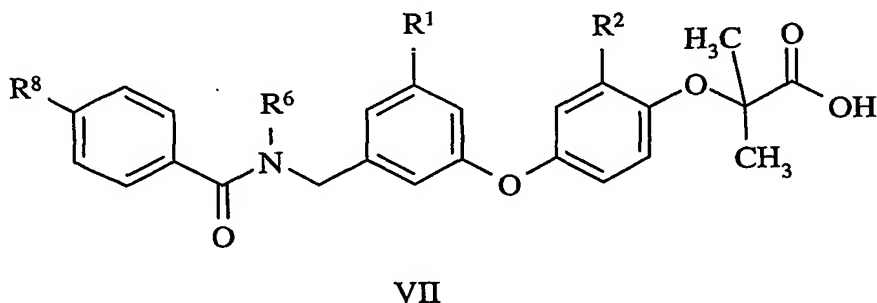
hydrogen, F, Cl, Br, OMe,  $CF_3$ ,  $OCF_3$ ,  $SCH_3$ ,  $NO_2$ , cyano, methyl, ethyl, isobutyl, isopropyl or *tert*-butyl.

10 Yet more preferred embodiment of the present invention is the compound having a structural formula VI,



or a pharmaceutically acceptable salt or stereoisomer thereof.

15 Yet another preferred embodiment of the present invention is the compound having a structural formula VII,



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$R^1$  and  $R^2$  are each independently: hydrogen, halo or  $C_1$ - $C_4$  alkyl;

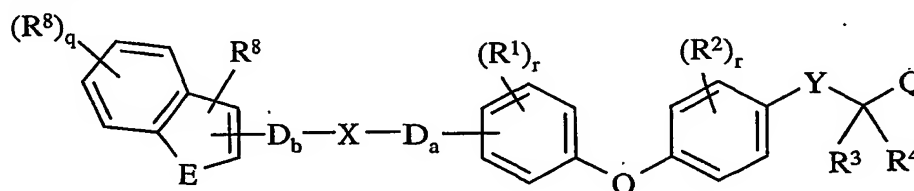
$R^6$  is: hydrogen or  $C_1$ - $C_4$  alkyl;

$R^8$  is: hydrogen, halo, haloalkyl or haloalkyloxy, cyano, nitro,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy or  $SR^9$ ; and

5  $R^9$  is: hydrogen or  $C_1$ - $C_4$  alkyl or  $C_3$ - $C_6$  cycloalkyl.

The compound as recited above in formula VII, wherein  $R^1$ ,  $R^2$  and  $R^6$  are each independently hydrogen or methyl; and  $R^8$  is hydrogen, F, Cl, Br, OMe,  $CF_3$ ,  $OCF_3$ ,  $SCH_3$ ,  $NO_2$ , methyl, ethyl, isobutyl, isopropyl or *tert*-butyl.

10 Yet another preferred embodiment of the present invention is the compound having a structural formula VIII,



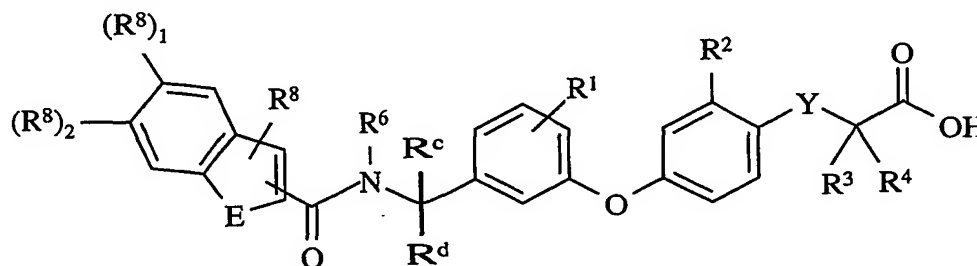
VIII

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

$q$  is 1, 2, 3 or 4; and

15  $E$  is S, O or  $NR^{10}$  wherein  $R^{10}$  is hydrogen or  $C_1$ - $C_4$  alkyl.

Yet another preferred embodiment of the present invention is the compound having a structural formula IX,



IX

20 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

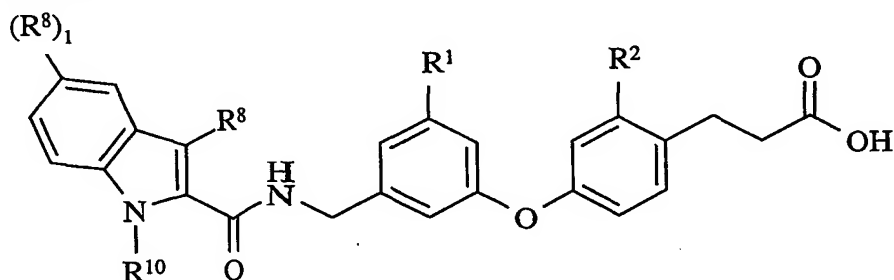
$Y$  is: O or  $CH_2$ ;

$E$  is: S, O, NH or  $NCH_3$ ,  $NCH_2CH_3$ ;

$R^1$  is: hydrogen,  $C_1$ - $C_4$  alkyl, halo or haloalkyl;

$R^2$ ,  $R^3$  and  $R^4$ ,  $R^6$ ,  $R^c$  and  $R^d$  are each independently: hydrogen or  $C_1$ - $C_4$  alkyl;  
 $(R^8)_1$  and  $(R^8)_2$  are each independently: hydrogen, halo, haloalkyl, haloalkyloxy, cyano, nitro,  $C_1$ - $C_6$  alkyl or  $C_1$ - $C_6$  alkoxy; and  
 $R^8$  is: hydrogen or  $C_1$ - $C_4$  alkyl.

5 Yet another preferred embodiment of the present invention is the compound having a structural formula X,

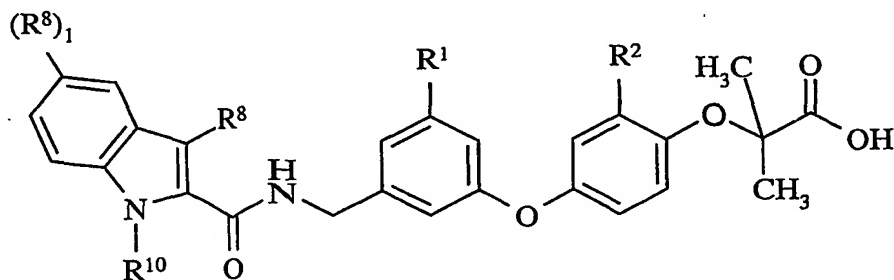


X

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

10  $R^1$  and  $R^2$  are each independently: hydrogen, halo or  $C_1$ - $C_4$  alkyl;  
 $(R^8)_1$  is: hydrogen, F, Cl, Br, OMe,  $CF_3$ ,  $OCF_3$ ,  $SCH_3$ ,  $NO_2$ , cyano, nitro, methyl, ethyl, isobutyl, isopropyl or *tert*-butyl;  
 $R^8$  is: hydrogen, methyl, ethyl or propyl; and  
 $R^{10}$  is: hydrogen, methyl or ethyl.

15 Yet another preferred embodiment of the present invention is the compound having a structural formula XI,



XI

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

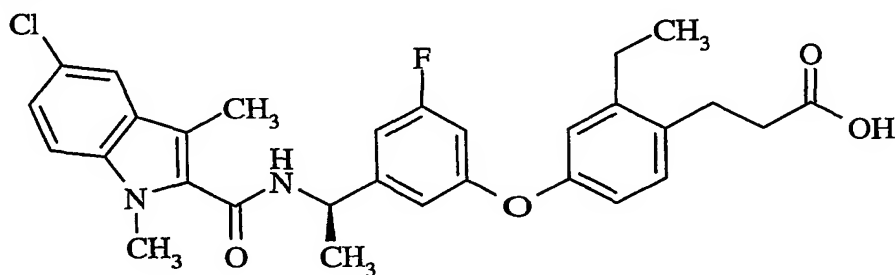
20  $R^1$  and  $R^2$  are each independently: hydrogen, halo or  $C_1$ - $C_4$  alkyl;

(R<sup>8</sup>)<sub>1</sub> is: hydrogen, F, Cl, Br, OMe, CF<sub>3</sub>, OCF<sub>3</sub>, SCH<sub>3</sub>, NO<sub>2</sub>, cyano, nitro, methyl, ethyl, isobutyl, isopropyl or *tert*-butyl;

R<sup>8</sup> is: hydrogen, methyl, ethyl or propyl; and

R<sup>10</sup> is: hydrogen, methyl or ethyl.

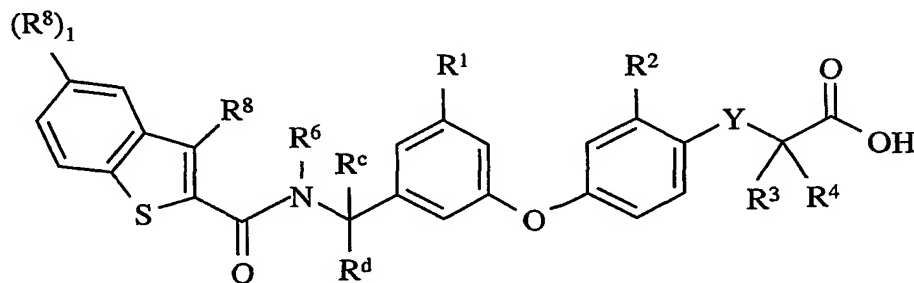
5 Yet more preferred embodiment of the present invention is the compound having a structural formula XII,



XII

or a pharmaceutically acceptable salt.

10 Yet another preferred embodiment of the present invention is the compound having a structural formula XIII,



XIII

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

15 Y is: O or CH<sub>2</sub>;

R<sup>1</sup> is: hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, halo or haloalkyl;

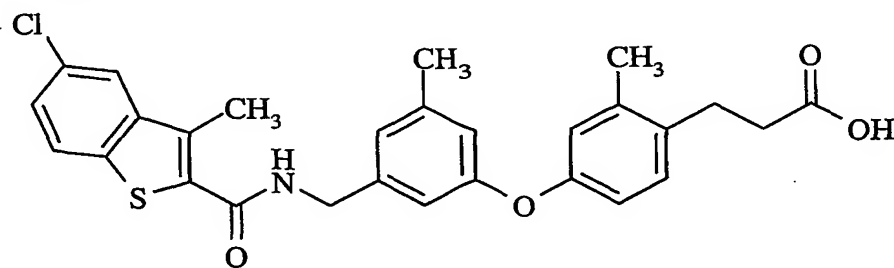
R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>c</sup> and R<sup>d</sup> are each independently: hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>8</sup> are each independently: hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl; and

20 (R<sup>8</sup>)<sub>1</sub> is: hydrogen, halo, haloalkyl or haloalkyloxy, cyano, nitroC<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>1</sub>-C<sub>6</sub> alkoxy.

The compound as recited above in formula XIII, wherein Y is O or CH<sub>2</sub>; R<sup>1</sup> is hydrogen, methyl, F, Br or Cl; R<sup>2</sup> is hydrogen, methyl or ethyl; R<sup>3</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>8</sup>, R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen or methyl; and (R<sup>8</sup>)<sub>1</sub> is hydrogen, F, Cl, Br, OMe, CF<sub>3</sub>, OCF<sub>3</sub>, SCH<sub>3</sub>, NO<sub>2</sub>, cyano, nitro, methyl, ethyl, isobutyl, isopropyl or *tert*-butyl.

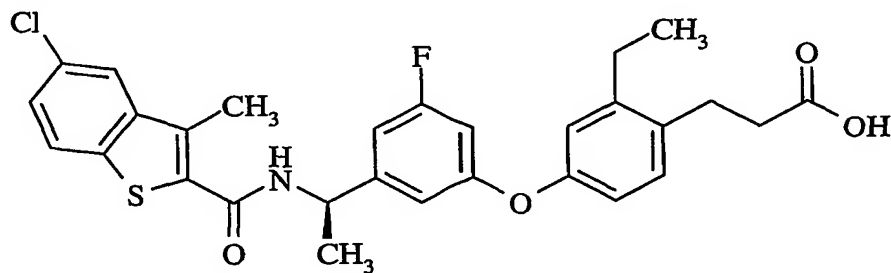
Yet another preferred embodiment of the present invention is the compound having a structural formula XIV,



XIV

or a pharmaceutically acceptable salt.

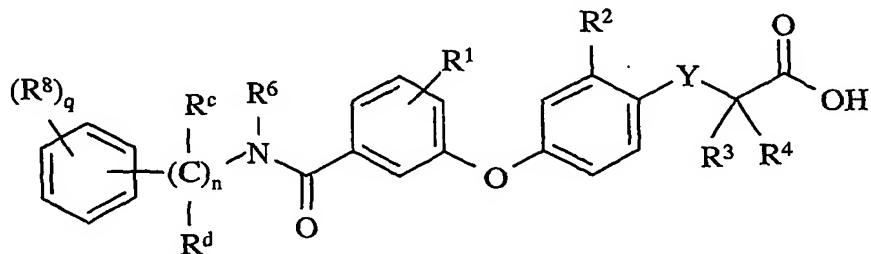
Yet more preferred embodiment of the present invention is the compound having a structural formula XV,



XV

or a pharmaceutically acceptable salt.

Yet another preferred embodiment of the present invention is the compound having a structural formula XVI,

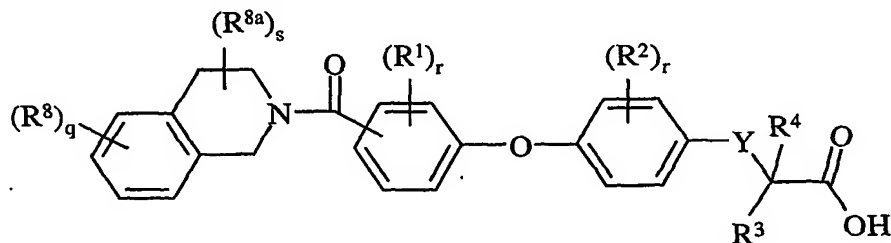


XVI

- 5 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein  
n is 1, 2, 3, or 4.

The compound as recited above in formula XVI, wherein Y is O or CH<sub>2</sub>;  
R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>c</sup> and R<sup>d</sup> are each independently hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl; n is 1 or 2; R<sup>6</sup> is  
hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or arylalkyl; and R<sup>8</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo or haloalkyl.

- 10 Yet another preferred embodiment of the present invention is the  
compound having a structural formula XVII,

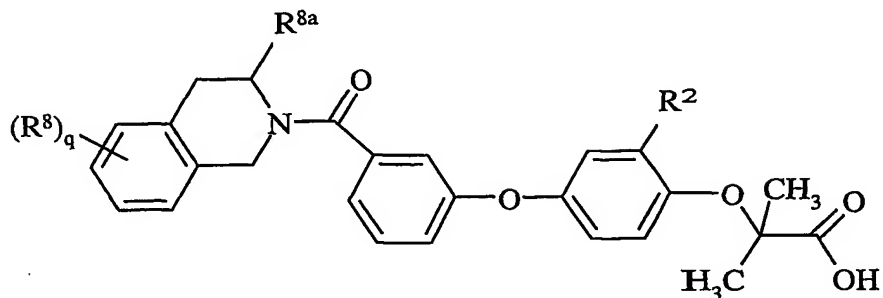


XVII

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

- 15 R<sup>8a</sup> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl or aryl; and s is 1, 2, 3, 4, 5 or 6.

Yet another preferred embodiment of the present invention is the compound having a structural formula XVIII,



XVIII

5 or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

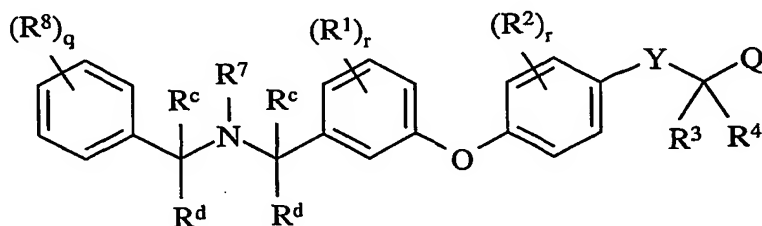
$R^2$  is: hydrogen or  $C_1$ - $C_4$  alkyl,

$R^8$  is: hydrogen,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halo, haloalkyl or haloalkyloxy;

$R^{8a}$  is: hydrogen, methyl, or phenyl; and

$q$  is: 1 or 2.

10 Yet another preferred embodiment of the present invention is the compound having a structural formula XIX,



XIX

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

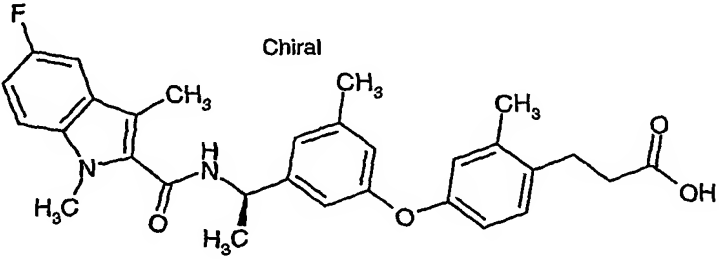
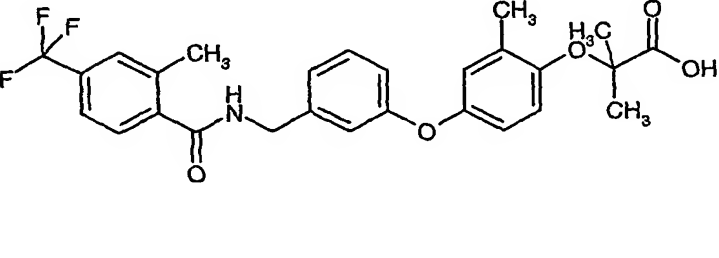
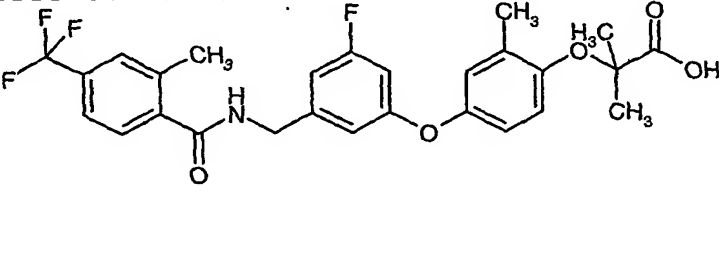
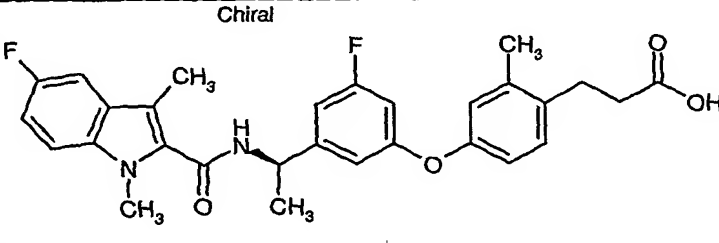
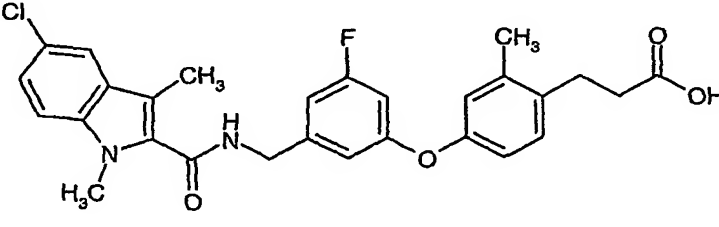
15 The compound as recited above in formula XIX, wherein Q is COOH;  $R^7$  is hydrogen, methanesulfonyl or acetyl; and  $R^c$  and  $R^d$  are each hydrogen.

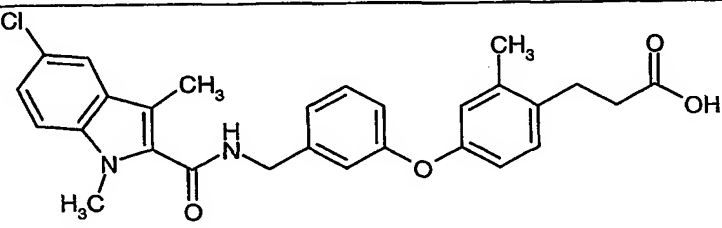
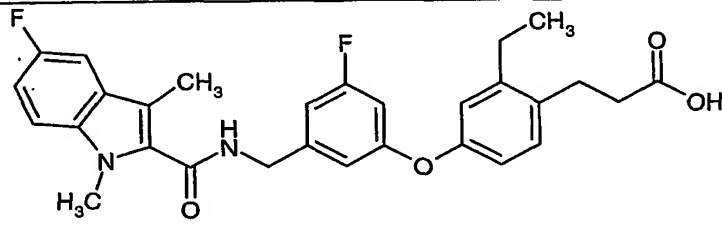
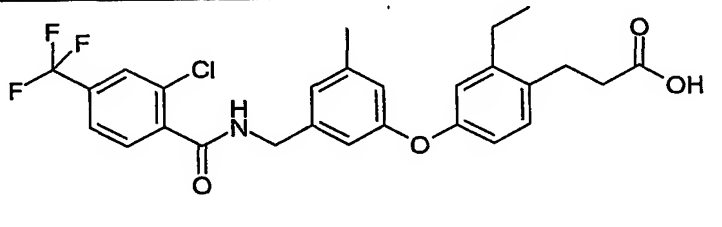


Yet more preferred embodiment of the present invention is the compound selected from the group consisting of:

No	Structure	Name
1		2-(4-{3-[(2-Chloro-4-trifluoromethyl-benzoylamino)-methyl]-5-fluorophenoxy}-2-methylphenoxy)-2-methylpropionic acid
2		3-[4-(3-{[(5-Chloro-1H-indole-2-carbonyl)-amino]-methyl}-5-fluorophenoxy)-2-methylphenyl]-propionic acid
3		2-(4-{3-Fluoro-5-[1-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methylphenoxy)-2-methylpropionic acid (isomer 1)
4		2-[4-(3-{[(5-Chloro-3-methylbenzo[b]thiophene-2-carbonyl)-amino]-methyl}-5-methylphenoxy)-2-methylphenoxy]-2-methylpropionic acid
5		( R )-3-[4-(3-{1-[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-fluorophenoxy)-2-methylphenyl]-propionic acid

No	Structure	Name
6		3-(2-Ethyl-4-{3-fluoro-5-[(2-methyl-4-trifluoromethylbenzoylamino)-methyl]-phenoxy}-phenyl)-propionic acid
7		2-(4-{3-[(2-Fluoro-4-trifluoromethylbenzoylamino)-methyl]-5-methylphenoxy}-2-methylphenoxy)-2-methylpropionic acid
8		( R )-2-[4-(3-{[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl}-5-methylphenoxy)-2-methylphenoxy]-2-methylpropionic acid
9		3-[4-(3-Fluoro-5-{[(5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-methyl}-phenyl)-2-methylphenyl]-propionic acid
10		2-[4-(3-Fluoro-5-{[(5-fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl}-phenoxy)-2-methylphenoxy]-2-methylpropionic acid

No	Structure	Name
11		( R ) -3-[4-(3-{1-[(5-Fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-methylphenoxy)-2-methylphenyl]-propionic acid
12		2-Methyl-2-(2-methyl-4-{3-[(2-methyl-4-trifluoromethylbenzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid
13		2-(4-{3-Fluoro-5-[(2-methyl-4-trifluoromethylbenzoylamino)-methyl]-phenoxy}-2-methylphenoxy)-2-methylpropionic acid
14		( R ) -3-[4-(3-Fluoro-5-{1-[(5-fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methylphenyl]-propionic acid
15		3-[4-(3-{[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl}-5-fluorophenoxy)-2-methylphenyl]-propionic acid

No	Structure	Name
16		3-[4-(3-{{[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl}-phenoxy)-2-methyl-phenyl]-propionic acid
17		3-[2-Ethyl-4-(3-fluoro-5-{{[(5-fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl}-phenoxy)-phenyl]-propionic acid
18		3-(4-{3-[(2-Chloro-4-trifluoromethyl-benzoylamino)-methyl]-5-methyl-phenoxy}-2-ethyl-phenyl)-propionic acid

Also encompassed by the present invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of the present invention or a pharmaceutically acceptable salt, solvate or hydrate thereof.

5 Also encompassed by the present invention is a pharmaceutical composition comprising: (1) a compound of the present invention or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof; (2) a second therapeutic agent selected from the group consisting of insulin sensitizers, sulfonylureas, biguanides, meglitinides, thiazolidinediones,  $\alpha$ -glucosidase inhibitors, insulin  
 10 secretagogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acyl CoA:cholesterol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin; and (3) optionally a pharmaceutically acceptable carrier.

Also encompassed by the present invention is a method of modulating a  
 15 peroxisome proliferator activated receptor (PPAR) comprising the step of contacting the

receptor with a compound of the present invention or a pharmaceutically acceptable salt, solvate or hydrate thereof.

The method recited above, wherein the PPAR is an alpha ( $\alpha$ )-receptor.

The method recited above, wherein the PPAR is a gamma ( $\gamma$ )-receptor.

5 The method recited above, wherein the PPAR is a delta ( $\delta$ )-receptor.

The method recited above, wherein the PPAR is a gamma/delta ( $\gamma/\delta$ )-receptor.

The method recited above, wherein the PPAR is an alpha, gamma and delta ( $\alpha/\gamma/\delta$ )-receptor.

10 Also encompassed by the present invention is a method for treating and/or preventing a PPAR- $\gamma$  mediated disease or condition in a mammal comprising the step of administering an effective amount of a compound of the present invention.

Also encompassed by the present invention is a method for treating and/or preventing a PPAR- $\delta$  mediated disease or condition in a mammal comprising the step of administering an effective amount of a compound of the present invention.

15 Also encompassed by the present invention is a method for treating and/or preventing a PPAR- $\gamma/\delta$  mediated disease or condition in a mammal comprising the step of administering an effective amount of a compound of the present invention.

Also encompassed by the present invention is a method for treating and/or preventing a PPAR- $\alpha/\gamma/\delta$  mediated disease or condition in a mammal comprising the step of administering an effective amount of a compound of the present invention.

20 Also encompassed by the present invention is a method for lowering blood-glucose in a mammal comprising the step of administering an effective amount of a compound of the present invention.

25 Also encompassed by the present invention is a method of treating and/or preventing disease or condition in a mammal selected from the group consisting of hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, anorexia nervosa,  
30 cardiovascular disease and other diseases where insulin resistance is a component,

comprising the step of administering an effective amount of a compound of a compound of the present invention.

Also encompassed by the present invention is a method of treating and/or preventing diabetes mellitus in a mammal comprising the step of administering to a mammal a therapeutically effective amount of a compound of the present invention.

Also encompassed by the present invention is a method of treating and/or preventing cardiovascular disease in a mammal comprising the step of administering to a mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

Also encompassed by the present invention is a method of treating and/or preventing syndrome X in a mammal comprising the step of administering to the mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

Also encompassed by the present invention is a method of treating and/or preventing disease or condition in a mammal selected from the group consisting of hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertension, obesity, anorexia bulimia, anorexia nervosa, cardiovascular disease and other diseases where insulin resistance is a component, comprising the step of administering an effective amount of a compound of the present invention, and an effective amount of second therapeutic agent selected from the group consisting of insulin sensitizers, sulfonylureas, biguanides, meglitinides, thiazolidinediones,  $\alpha$ -glucosidase inhibitors, insulin secretagogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acyl CoA:cholesterol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin.

Also encompassed by the present invention is use of a compound of the present invention and a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, for the manufacture of a medicament for the treatment of a condition modulated by a PPAR.

The terms used to describe the present invention have the following meanings unless otherwise indicated.

An "aliphatic group" is non-aromatic consisting solely of carbon and hydrogen and may optionally contain one or more units of unsaturation, e.g., double-  
5 bonds ("alkenyl") and/or triple-bonds ("alkynyl"). An aliphatic group may be straight chained, branched or cyclic. When straight chained or branched, an aliphatic group typically contains between about 1 and about 12 carbon atoms, more typically between about 1 and about 6 carbon atoms. When cyclic, an aliphatic group typically contains  
10 carbon atoms. Aliphatic groups are preferably C<sub>1</sub>-C<sub>12</sub> straight chained and/or branched alkyl groups (i.e., completely saturated aliphatic groups), more preferably C<sub>1</sub>-C<sub>6</sub> straight chained and/or branched alkyl groups. Examples include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl and the like.

The term "alkyl," unless otherwise indicated, refers to those alkyl groups  
15 of a designated number of carbon atoms of either a straight or branched saturated configuration, including substituted alkyl. The term "alkyl" used herein also includes "alkylene group" of either straight or branched saturated configuration, including substituted alkylene. Examples of "alkyl" include, but are not limited to: methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl and *tert*-butyl, pentyl, hexyl, isopentyl and  
20 the like. Examples of "alkylene group" is  $-[C(R^c)(R^d)]_n-$  where *n* is a positive integer, and R<sup>c</sup> and R<sup>d</sup> are independently hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl. Preferably, *n* is an integer from about 1 to about 6, and more preferably from about 1 to about 4. A "branched (or substituted) alkylene group" is an alkylene group in which one or more methylene hydrogen atoms are replaced with a substituent, such as methyl, ethyl or the like. Alkyl  
25 as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl,  
30 heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

The term "alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

5           The term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, and the like. Alkoxy as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

10           The term "cycloalkyl" refers to a saturated or partially saturated carbocycle containing one or more rings of from 3 to 12 carbon atoms, more typically 3 to 6 carbon atoms. Examples of cycloalkyl includes, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and the like. Cycloalkyl as defined above may also include a tricycle, such as adamantyl. Cycloalkyl as defined above may be  
15 optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "halo" refers to fluoro, chloro, bromo and iodo.

The term "haloalkyl" is a C<sub>1</sub>-C<sub>6</sub> alkyl group, which is substituted with one or more halo atoms selected from F, Br, Cl and I. Examples of haloalkyl group are  
20 trifluoromethyl, CH<sub>2</sub>CF<sub>3</sub> and the like.

The term "haloalkyloxy" represents a C<sub>1</sub>-C<sub>6</sub> haloalkyl group attached through an oxygen bridge, such as OCF<sub>3</sub>. The "haloalkyloxy" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

25           The term "aryl" includes carbocyclic aromatic ring systems (e.g. phenyl), fused polycyclic aromatic ring systems (e.g. naphthyl and anthracenyl) and aromatic ring systems fused to carbocyclic non-aromatic ring systems (e.g., 1,2,3,4-tetrahydronaphthyl). The "aryl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

30           The term "aryloxy" represents an aryl group attached through an oxygen bridge, such as phenoxy (-O-phenyl). The "aryloxy" as defined above may be optionally



substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "heteroaryl" group, as used herein, is an aromatic ring system having at least one heteroatom such as nitrogen, sulfur or oxygen and includes  
5 monocyclic, bicyclic or tricyclic aromatic ring of 5- to 14-carbon atoms containing one or more heteroatoms selected from O, N, or S. The heteroaryl as defined above also includes heteroaryl fused with another heteroaryl, aryl fused with heteroaryl or aryl fused with heterocyclyl as defined herein. The "heteroaryl" may also be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

10 Examples of heteroaryl are, but are not limited to: furanyl, thienyl (also referred to as "thiophenyl"), thiazolyl, imidazolyl, indolyl, isoindolyl, isooxazolyl, oxazolyl, pyrazolyl, pyrrolyl, pyrazinyl, pyridyl, pyrimidyl, pyrimidinyl and purinyl, cinnolinyl, benzofuranyl, benzoimidazolyl, benzothienyl (or benzothiophenyl), benzotriazolyl, benzoxazolyl, quinolinyl, isoxazolyl, isoquinolinyl 1,4 benzodioxan, or 2,3-dihydrobenzofuranyl and the  
15 like.

The term "heterocyclyl" refers to a non-aromatic ring which contains one or more heteroatoms selected from O, N or S, which includes a monocyclic, bicyclic or tricyclic ring of 5- to 14-carbon atoms containing one or more heteroatoms selected from O, N or S. The "heterocyclyl" as defined above may be optionally substituted with a  
20 designated number of substituents as set forth in the embodiment recited above. Examples of heterocyclyl include, but are not limited to, morpholine, piperidine, piperazine, pyrrolidine, and thiomorpholine.

The term "carbocyclyl" (also referred as "nonaromatic carbocyclic ring") refers to a saturated or partially saturated nonaromatic carbocyclic ring. Examples of  
25 carbocyclyl are, but are not limited to, cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl and the like.

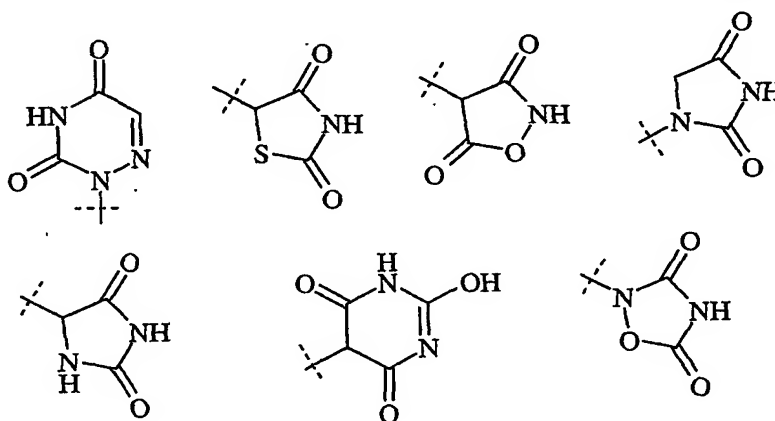
An "arylalkyl" as used herein is an aryl substituent that is linked to a compound by an alkyl group having from one to six carbon atoms (e.g., C<sub>1</sub>-C<sub>6</sub> alkyl-aryl). The "arylalkyl" as defined above may be optionally substituted with a designated number  
30 of substituents as set forth in the embodiment recited above.

The "acyl" represent an "alkyl-C(=O)-" group. Preferred acyl group are those in which the alkyl group is lower alkyl, such C<sub>1</sub>-C<sub>6</sub> alkyl. Example of "acyl" is acetyl.

5 A "sulfonyl" is represent an "alkyl-S(O)<sub>2</sub>-" group Preferred sulfonyl group are those in which the alkyl group is lower alkyl, such C<sub>1</sub>-C<sub>6</sub> alkyl. Example of "sulfonyl" is mathanesulfonyl, ethansulfonyl and the like.

The "aminoalkyl" as used herein contains both a basic amino group (NH<sub>2</sub>) and an alkyl group as defined above.

10 The term R<sup>5A</sup> (or acid bioisosteres) as used herein includes, but are not limited to, carboxamide, sulfonamide, acylsulfonamide, tetrazole or the following moiety.



Carboxamide, sulfonamide, acylsulfonamide and tetrazole may be optionally substituted with one or more suitable substituents selected from haloalkyl, aryl, heteroaryl, and C<sub>1</sub>-C<sub>6</sub> alkyl. The heteroalkyl, aryl, heteroaryl and alkyl may further optionally substituted with one or more substituents selected from the list provided for R<sup>8</sup>. The examples of R<sup>5A</sup> are, but not limited to, hydroxamic acid, acyl cyanamide, tetrazoles, sulfinylazole, sulfonylazole, 3-hydroxyisoxazole, hydroxythiadiazole, sulphonate and acylsulfonamide.

The term "active ingredient" means the compounds generically described by Formula I as well as the salts, solvates and prodrugs of such compounds.

20 The term "pharmaceutically acceptable" means that the carrier, diluents, excipients and salt must be compatible with the other ingredients of the composition, and not deleterious to the recipient thereof. Pharmaceutical compositions of the present invention are prepared by procedures known in the art using well-known and readily available ingredients.

"Preventing" refers to reducing the likelihood that the recipient will incur or develop any of the pathological conditions described herein.

"Treating" refers to mediating a disease and/or condition, and preventing and/or mitigating its further progression or ameliorating the symptoms associated with the disease or condition.

"Pharmaceutically-effective amount" means that amount of a compound of the present invention, or of its salt, solvate, hydrate or prodrug thereof that will elicit the biological or medical response of a tissue, system or mammal. Such an amount can be administered prophylactically to a patient thought to be susceptible to development of a disease or condition. Such amount when administered prophylactically to a patient can also be effective to prevent or lessen the severity of the mediated condition. Such an amount is intended to include an amount, which is sufficient to modulate a PPAR receptor such as a PPAR $\alpha$ , PPAR $\gamma$ , PPAR $\delta$  or PPAR $\gamma/\delta$  receptor to mediate a disease or condition. Conditions mediated by PPAR receptors include, for example, diabetes mellitus, cardiovascular disease, Syndrome X, obesity and gastrointestinal disease. Additional conditions associated with the modulation of a PPAR receptor include inflammation related conditions, which include, for example, IBD (inflammatory bowel disease), rheumatoid arthritis, psoriasis, Alzheimer's disease, Crohn's disease and ischemia reperfusion injury (stroke and myocardial infarction).

A "mammal" is an individual animal that is a member of the taxonomic class Mammalia. The class Mammalia includes humans, monkeys, chimpanzees, gorillas, cattle, swine, horses, sheep, dogs, cats, mice, rats and the like.

Administration to a human is most preferred. A human to whom the compounds and compositions of the present invention are administered has a disease or condition in which control blood glucose levels are not adequately controlled without medical intervention, but wherein there is endogenous insulin present in the human's blood. Non-insulin dependent diabetes mellitus (NIDDM) is a chronic disease or condition characterized by the presence of insulin in the blood, even at levels above normal, but resistance or lack of sensitivity to insulin action at the tissues.

Those skilled in the art will recognize that stereocenters exist in compound of the present invention. Accordingly, the present invention includes all possible

stereoisomers and geometric isomers of the presently claimed compounds including racemic compounds and the optically active isomers.

The compounds of the present invention contain one or more chiral centers and exist in different optically active forms. When compounds of the present invention contain one chiral center, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers, such as racemic mixtures. Resolution of the final product, an intermediate or a starting material may be effected by any suitable method known in the art, for example by formation of diastereoisomeric salts which may be separated by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated by crystallization and gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent such as enzymatic esterification; and gas-liquid or liquid chromatography in a chiral environment such as on a chiral support, for example silica with a bound chiral ligand or in the presence of a chiral solvent. See also *Stereochemistry of Carbon Compounds* by E.L. Eliel (Mcgraw Hill, 1962) and *Tables of Resolving Agents* by S. H. Wilen. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

When a compound of the present invention has more than one chiral substituents, it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of formula I and mixtures thereof.

Certain compounds of the present invention may exist in different stable conformational forms, which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring

strain, may permit separation of different conformers. The present invention includes each conformational isomer of compounds of formula I and mixtures thereof.

Certain compound of the present invention may exist in zwitterionic form, and the present invention includes each zwitterionic form of compounds of formula I and mixtures thereof.

Certain compounds of the present invention and their salts may exist in more than one crystal form. Polymorphs of compounds of formula I form part of the present invention and may be prepared by crystallization of a compound of formula I under different conditions, such as using different solvents or different solvent mixtures for recrystallization; crystallization at different temperatures; and various modes of cooling ranging from very fast to very slow cooling during crystallization. Polymorphs may also be obtained by heating or melting a compound of formula I followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or other available techniques.

Certain compounds of the present invention and their salts may exist in more than one crystal form, which includes each crystal form and mixtures thereof.

Certain compounds of the present invention and their salts may also exist in the form of solvates, for example hydrates, and thus the present invention includes each solvate and mixtures thereof.

"Pharmaceutically-acceptable salt" refers to salts of the compounds of formula I, which are substantially non-toxic to mammals. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral, organic acid: an organic base or inorganic base. Such salts are known as base addition salts, respectively. It should be recognized that the particular counterion forming a part of any salt of the present invention is not of a critical nature so long as the salt as a whole is pharmaceutically acceptable and the counterion does not contribute undesired qualities to the salt as a whole.

By virtue of its acidic moiety, a compound of the present invention forms salts with pharmaceutically acceptable bases. Some examples of base addition salts include metal salts such as aluminum; alkali metal salts such as lithium, sodium or

potassium; and alkaline earth metal salts such as calcium, magnesium, ammonium, or substituted ammonium salts. Examples of substituted ammonium salts include, for instance, those with lower alkylamines such as trimethylamine and triethylamine; hydroxyalkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine; cycloalkylamines such as bicyclohexylamine or dibenzylpiperidine, N-benzyl- $\beta$ -phenethylamine, dehydroabietylamine, N,N'-bisdehydro-abietylamine, glucamine, N-piperazine methylglucamine; bases of the pyridine type such as pyridine, collidine, quinine or quinoline; and salts of basic amino acids such as lysine and arginine.

Examples of inorganic bases include, without limitation, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

Compounds of the present invention, which are substituted with a basic group, may exist as salts with pharmaceutically acceptable acids. The present invention includes such salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [e.g. (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in the art.

The compounds of the present invention (or salt or prodrug, etc.) may also form a solvate with water (e.g., hydrate) or an organic solvent, and the present invention encompasses any solvate, hydrate or any mixtures thereof.

The compounds of present invention, which bind to and activate the PPARs, lower one or more of glucose, insulin, triglycerides, fatty acids and/or cholesterol, and are therefore useful for the treatment and/or prevention of hyperglycemia, dyslipidemia and in particular Type II diabetes as well as other diseases including syndrome X, Type I diabetes, hypertriglyceridemia, insulin resistance, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, heart failure, coagulopathy, hypertension, and cardiovascular diseases, especially arteriosclerosis. In addition, these compounds are indicated to be useful for the regulation of appetite and food intake in subjects suffering from disorders such as obesity, anorexia bulimia and anorexia nervosa.

The compounds and compositions of the present invention are also useful to treat acute or transient disorders in insulin sensitivity, which sometimes occurs following a surgery, trauma, myocardial infarction and the like. The compounds and compositions of the present invention are also useful for lowering serum triglyceride levels. Elevated triglyceride level, whether caused by genetic predisposition or by a high fat diet, is a risk factor for the development of heart disease, stroke, and circulatory system disorders and diseases. The physician of ordinary skill will know how to identify humans who can benefit from administration of the compounds and compositions of the present invention.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycemia in a human or non-human mammal which comprises administering an effective, non-toxic amount of a compound of formula I, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a hyperglycemic human or non-human mammal in need thereof.

The compounds of the present invention are useful as therapeutic substances in preventing or treating Syndrome X, diabetes mellitus and related endocrine and cardiovascular disorders and diseases in human or non-human animals.

The present invention also relates to the use of a compound of formula I as described above for the manufacture of a medicament for treating a PPAR $\gamma$  or PPAR $\delta$  mediated condition, separately or in combination.

A therapeutically effective amount of a compound of the present invention can be used for the preparation of a medicament useful for treating Syndrome X, diabetes, treating obesity, lowering tryglyceride levels, raising the plasma level of high density lipoprotein, and for treating, preventing or reducing the risk of developing arteriosclerosis, and for preventing or reducing the risk of having a first or subsequent atherosclerotic disease event in mammals, particularly in humans. In general, a therapeutically effective amount of a compound of formula I of the present invention typically reduces serum glucose levels, more specifically HbA1c, of a patient by about 0.7% or more; typically reduces serum triglyceride levels of a patient by about 20% or

more; and increases serum HDL levels in a patient. Preferably, HDL levels can be increased by about 30% or more.

Additionally, an effective amount of a compound of the present invention and a therapeutically effective amount of one or more active agents selected from antihyperlipidemic agent, plasma HDL-raising agents, antihypercholesterolemic agents, 5 fibrates, vitamins, aspirin, insulin secretagogues, insulin and the like can be used together for the preparation of a medicament useful for the above described treatments.

Advantageously, compositions containing the compound of the present invention or their salts may be provided in dosage unit form, preferably each dosage unit 10 containing from about 1 to about 500 mg. It is understood that the amount of the compounds or compounds of the present invention that will be administered is determined by a physician considering of all the relevant circumstances.

Syndrome X includes pre-diabetic insulin resistance syndrome and the resulting complications thereof, insulin resistance, non-insulin dependent diabetes, 15 dyslipidemia, hyperglycemia obesity, coagulopathy, hypertension and other complications associated with diabetes. The methods and treatments mentioned herein include the above and encompass the treatment and/or prophylaxis of any one of or any combination of the following: pre-diabetic insulin resistance syndrome, the resulting complications thereof, insulin resistance, Type II or non-insulin dependent diabetes, 20 dyslipidemia, hyperglycemia, obesity and the complications associated with diabetes including cardiovascular disease, especially arteriosclerosis.

The compositions are formulated and administered in the same general manner as detailed herein. The compounds of the present invention may be used effectively alone or in combination with one or more additional active agents depending 25 on the desired target therapy. Combination therapy includes administration of a single pharmaceutical dosage composition, which contains a compound of the present invention and one or more additional active agents, as well as administration of a compound of the present invention and each active agent in its own separate pharmaceutical dosage. For example, a compound of the present invention or thereof and an insulin secretagogue 30 such as biguanides, meglitinides, thiazolidinediones, sulfonylureas, insulin or  $\alpha$ -glucosidase inhibitors can be administered to the patient together in a single oral dosage



composition such as a tablet or capsule, or each agent administered in separate oral dosages. Where separate dosages are used, a compound of the present invention and one or more additional active agents can be administered at essentially the same time, i.e., concurrently or at separately staggered times, i.e., sequentially; combination therapy is understood to include all these regimens.

An example of combination treatment or prevention of arteriosclerosis may involve administration of a compound of the present invention or salts thereof in combination with one or more of second active therapeutic agents: antihyperlipidemic agents; plasma HDL-raising agents; antihypercholesterolemic agents, fibrates, vitamins, aspirin and the like. As noted above, the compounds of the present invention can be administered in combination with more than one additional active agent.

Another example of combination therapy can be seen in treating diabetes and related disorders wherein the compounds of the present invention or salts thereof can be effectively used in combination with second active therapeutic, such as sulfonylureas, biguanides, meglitinides, thiazolidinediones,  $\alpha$ -glucosidase inhibitors, other insulin secretagogues, insulin as well as the active agents discussed above for treating arteriosclerosis.

The examples of second therapeutic agents are insulin sensitizers, PPAR $\gamma$  agonists, glitazones, troglitazone, pioglitazone, englitazone, MCC-555, BRL 49653, biguanides, metformin, phenformin, insulin, insulin minetics, sulfonylureas, tolbutamide, glipizide, alpha-glucosidase inhibitors, acarbose, cholesterol lowering agent, HMG-CoA reductase inhibitors, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, other statins, sequestrates, cholestyramine, colestipol, dialkylaminoalkyl derivatives of a cross-linked dextran, nicotiny alcohol, nicotinic acid: a nicotinic acid salt, PPAR $\alpha$  agonists, fenofibric acid derivatives, gemfibrozil, clofibrate, fenofibrate, benzfibrate, inhibitors of cholesterol absorption, beta-sitosterol, acyl CoA:cholesterol acyltransferase inhibitors, melinamide, probucol, PPAR $\delta$  agonists, antiobesity compounds, fenfluramine, dexfenfluramine, phentiramine, sulbitramine, orlistat, neuropeptide Y5 inhibitors,  $\beta_3$  adrenergic receptor agonists, and ileal bile acid transporter inhibitors.

The compounds of the present invention and their pharmaceutically acceptable salt, solvate or hydrate thereof have valuable pharmacological properties and can be used in pharmaceutical compositions containing a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, ester or prodrug thereof, in combination with one or more pharmaceutically acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, fillers, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, wetting agents, binders, disintegrating agents, encapsulating material and other conventional adjuvants. Proper excipient is dependent upon the route of administration chosen. Pharmaceutical compositions typically contain from about 1 to about 99 weight percent of the active ingredient, which is a compound of the present invention.

Preferably, the pharmaceutical formulation is in unit dosage form. A "unit dosage form" is a physically discrete unit containing a unit dose suitable for administration in human subjects or other mammals. For example, a unit dosage form can be a capsule or tablet, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more pharmaceutically acceptable excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

The dosage regimen utilizing the compounds of the present invention is selected by one of ordinary skill in the medical or veterinary arts considering various factors, such as without limitation, the species, age, weight, sex, medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed, and the like.

Preferably, the compounds of the present invention are administered in a single daily dose, or the total daily dose may be administered in divided doses of two, three or more times per day. Where delivery is via transdermal forms, administration is continuous.

Suitable routes of administration of pharmaceutical compositions of the present invention include, for example, oral, eye drop, rectal, transmucosal, topical or intestinal administration; parenteral delivery (bolus or infusion), including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraven-tricular, intravenous, intraperitoneal, intranasal, or intraocular injections. The compounds of the present invention can also be administered in a targeted drug delivery system, such as in a liposome coated with endothelial cell-specific antibody.

For oral administration, the compounds of the present invention can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the present invention to be Formulated as tablets, pills, powders, sachets, granules, dragees, capsules, liquids, elixirs, tinctures, gels, emulsions, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by combining the active compound with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores.

For oral administration in the form of a tablet or capsule, the active ingredient may be combined with an oral, non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, methyl cellulose, calcium carbonate, calcium phosphate, calcium sulfate, sodium carbonate, mannitol, sorbitol, and the like; together with, optionally, disintegrating agents, such as, without limitation, cross-linked polyvinyl pyrrolidone, maize, starch, methyl cellulose, agar, bentonite, xanthan gum, alginic acid: or a salt thereof such as sodium alginate, and the like; and, optionally, binding agents, for example, without limitation, gelatin, acacia, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethyl-cellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid: sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Solid forms include powders, tablets and capsules. A solid carrier can be one or more substances, which may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

In powders, the carrier is a finely divided solid, which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile liquids include suspensions, emulsions, syrups, and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations, which can be used orally, include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active

compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

All formulations for oral administration should be in dosages suitable for such administration. Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules.

For parental administration, the compounds of the present invention or salts thereof can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. Formulations for injection may be presented in unit dosage form, such as in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that each syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against any contamination. The carrier can be solvent or dispersion medium containing, for example, water, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

For buccal administration, the compositions may take the form of tablets or lozenges Formulated in a conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of a dry powder inhaler, or an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane,

5 dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

10 Pharmaceutical compositions of the present invention can be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

In making the compositions of the present invention, the active  
15 ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, lyophilized solid or paste, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups,  
20 aerosols (as a solid or in a liquid medium), or ointment, containing for example up to 10% by weight of the active compound. The compounds of the present invention are preferably formulated prior to administration.

#### Binding and Cotransfection Studies

25 The in vitro potency of compounds in modulating PPAR $\gamma$ , PPAR $\alpha$  and PPAR $\delta$  receptors are determined by the procedures detailed below. DNA-dependent binding (ABCD binding) is carried out using Scintillation Proximity Assay (SPA) technology with PPAR receptors. Tritium-labeled PPAR $\alpha$  and PPAR $\gamma$  agonists are used as radioligands for generating displacement curves and IC<sub>50</sub> values with compounds of  
30 the present invention. Cotransfection assays are carried out in CV-1 cells. The reporter plasmid contains an acylCoA oxidase (AOX) PPRE and TK promoter upstream of the

luciferase reporter cDNA. Appropriate PPARs and RXR $\alpha$  are constitutively expressed using plasmids containing the CMV promoter. Since for PPAR $\alpha$  and PPAR $\beta$ , interference by endogenous PPAR $\gamma$  in CV-1 cells is an issue, in order to eliminate such interference, a GAL4 chimeric system is used in which the DNA binding domain of the transfected PPAR is replaced by that of GAL4, and the GAL4 response element is utilized in place of the AOX PPRE. Receptor activation by compounds of the present invention is determined relative to PPAR $\alpha$  agonist and PPAR $\gamma$  agonist reference molecules to obtain percent efficacies. EC<sub>50</sub> values are determined by computer fit to a concentration-response curve. A typical range for concentration determination is from 1nM to 10 $\mu$ M. For binding or cotransfection studies with receptors other than PPARs, similar assays are carried out using appropriate ligands, receptors, reporter constructs and etc. for that particular receptor. In some cases, a single high concentration of agonist (10  $\mu$ M) was used.

These studies are carried out to evaluate the ability of compounds of the present invention to bind to and/or activate various nuclear transcription factors, particularly huPPAR $\alpha$  ("hu" indicates "human"), huPPAR $\gamma$  and huPPAR $\delta$ . These studies provide in-vitro data concerning efficacy and selectivity of compounds of the present invention. Furthermore, binding and cotransfection data for compounds of the present invention are compared with corresponding data for reference compounds that act on either huPPAR $\alpha$  or huPPAR $\gamma$ . The typical range of concentration for binding is from 1nM to 10 $\mu$ M. The concentration of test compound required to effect 50% maximal activation of PPAR $\alpha$  (IC<sub>50 $\alpha$</sub> ) and PPAR $\gamma$  (IC<sub>50 $\gamma$</sub> ) is determined.

The compounds of the present invention, in general, have IC<sub>50</sub> or EC<sub>50</sub> in the range of about 1nM to about 1000 nM for either PPAR alpha, gamma or delta, preferably below about 50 nM for PPAR delta and below about 500 nM for PPAR gamma.

#### Evaluation of Triglyceride and Cholesterol Level in HuapoAI Transgenic Mice

Five to six week old male mice, transgenic for human apoAI [C57Bl/6-tgn(apoal)1rub, Jackson Laboratory, Bar Harbor, ME] are housed five per cage (10"x20"x8" with aspen chip bedding) with food (Purina 5001) and water available at all

times. After an acclimation period of 2 weeks, animals are individually identified by ear notches, weighed and assigned to groups based on body weight. Beginning the following morning, mice are dosed daily by oral gavage for 7 days using a 20 gauges, 1½" curved disposable feeding needle. Treatments are test compounds (30 mg/kg), a positive control (fenofibrate, 100 mg/kg) or vehicle [1% carboxymethylcellulose (w/v)/ 0.25% Tween80 (w/v); 0.2 ml/mouse]. Prior to termination on day 7, mice are weighed and dosed. Three hours after dosing, animals are anesthetized by inhalation of isoflurane (2-4%) and blood obtained via cardiac puncture (0.7-1.0 ml). Whole blood is transferred to serum separator tubes (Vacutainer SST), chilled on ice and permitted to clot. Serum is obtained after centrifugation at 4°C and frozen until analysis for triglycerides, total cholesterol, compound levels and serum lipoprotein profile by fast protein liquid chromatography (FPLC) coupled to an inline detection system. After sacrifice by cervical dislocation, the liver, heart and epididymal fat pads are excised and weighed.

The animals dosed with vehicle have average triglycerides values of about 60 to 80 mg/dl, which are reduced by the positive control fenofibrate (33-58 mg/dl with a mean reduction of 37%). The animals dosed with vehicle have average total serum cholesterol values of about 140 to 180 mg/dl, which are increased by fenofibrate (about 190 to 280 mg/dl with a mean elevation of 41%). When subject to FPLC analysis, pooled sera from vehicle-treated hu apoAI transgenic mice have a high-density lipoprotein cholesterol (HDLc) peak area, which ranges from 47v-sec to 62v-sec. Fenofibrate increases the amount of HDLc (68-96v-sec with a mean percent increase of 48%). Test compounds evaluated in terms of percent increase in the area under the curve.

Representative compounds of the present invention are tested using the above methods or substantially similar methods.

#### Evaluation of Glucose Levels in db/db Mice

Five week old male diabetic (db/db) mice [C57BlKs/j-m +/+ Lepr(db), Jackson Laboratory, Bar Harbor, ME] or lean littermates (db+) are housed 6 per cage (10"x20"x8" with aspen chip bedding) with food (Purina 5015) and water available at all times. After an acclimation period of 2 weeks, animals are individually identified by ear notches, weighed and bled via the tail vein for determination of initial glucose levels. Blood is collected (100 µl) from unfasted animals by wrapping each mouse in a towel,



cutting the tip of the tail with a scalpel, and milking blood from the tail into a heparinized capillary tube balanced on the edge of the bench. Sample is discharged into a heparinized microtainer with gel separator (VWR) and retained on ice. Plasma is obtained after centrifugation at 4°C and glucose is measured immediately. Remaining plasma is frozen until the completion of the experiment, and glucose and triglycerides are assayed in all samples. Animals are grouped based on initial glucose levels and body weights. Beginning the following morning, mice are dosed daily by oral gavage for 7 days using a 20 gauge, 1½" curved disposable feeding needle. Treatments are test compounds (30 mg/kg), a positive control agent (30 mg/kg) or vehicle [1% carboxymethylcellulose (w/v)/0.25% Tween80 (w/v); 0.3 ml/mouse]. On day 7, mice are weighed and bled (tail vein) for about 3 hours after dosing. Twenty-four hours after the 7<sup>th</sup> dose (i.e., day 8), animals are bled again (tail vein). Samples obtained from conscious animals on days 0, 7 and 8 are assayed for glucose. After 24 hour bleed, animals are weighed and dosed for the final time. Three hours after dosing on day 8, animals are anesthetized by inhalation of isoflurane, and blood obtained is via cardiac puncture (0.5-0.7 ml). Whole blood is transferred to serum separator tubes, chilled on ice and permitted to clot. Serum is obtained after centrifugation at 4°C and frozen until analysis for compound levels. After sacrifice by cervical dislocation, the liver, heart and epididymal fat pads are excised and weighed.

The animals dosed with vehicle have average triglycerides values of about 170 to 230 mg/dl, which are reduced by the positive PPAR $\gamma$  control (about 70 to 120 mg/dl with a mean reduction of 50%). Male db/db mice are hyperglycemic (average glucose of about 680 to 730 mg/dl on the 7<sup>th</sup> day of treatment), while lean animals have average glucose levels between about 190 and 230 mg/dl. Treatment with the positive control agent reduces glucose significantly (about 350 to 550 mg/dl with a mean decrease towards normalization of 56%).

Glucose is measured colorimetrically by using commercially purchased reagents (Sigma #315-500). According to the manufacturers, the procedures are modified from published work (McGowan et al. *Clin Chem*, 20:470-5 (1974) and Keston, A. Specific colorimetric enzymatic analytical reagents for glucose. Abstract of papers 129<sup>th</sup> Meeting ACS, 31C (1956).); and depend on the release of a mole of hydrogen peroxide

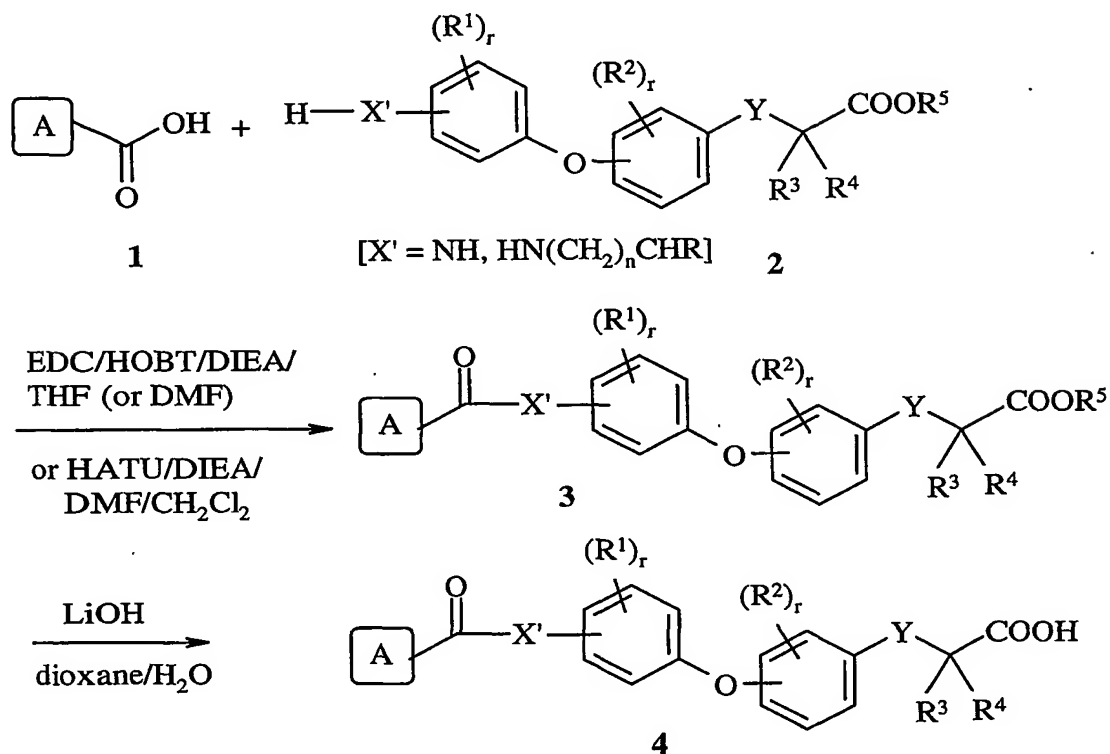
for each mole of analyte coupled with a color reaction first described by Trinder (Trinder, *P. Ann Clin Biochem*, 6:24 (1969)). The absorbance of the dye produced is linearly related to the analyte in the sample. The assays are further modified for use in a 96 well format. Standards (Sigma #339-11, Sigma #16-11, and Sigma #CC0534 for glucose, triglycerides and total cholesterol, respectively), quality control plasma (Sigma # A2034), and samples (2 or 5 µl/well) are measured in duplicate using 200 µl of reagent. An additional aliquot of sample, pipetted to a third well and diluted in 200 µl water, provided a blank for each specimen. Plates are incubated at room temperature (18, 15, and 10 minutes for glucose, triglycerides and total cholesterol, respectively) on a plate shaker and absorbance read at 500 nm (glucose and total cholesterol) or 540 nm (triglycerides) on a plate reader. Sample absorbance is compared to a standard curve (100-800, 10-500, and 100-400 mg/dl for glucose, triglycerides and total cholesterol, respectively). Values for the quality control sample are consistently within the expected range and the coefficient of variation for samples is below 10%. All samples from an experiment are assayed at the same time to minimize inter-assay variability.

Serum lipoproteins are separated and cholesterol is quantitated with an in-line detection system. Sample is applied to a Superose® 6 HR 10/30-size exclusion column (Amersham Pharmacia Biotech) and eluted with phosphate buffered saline-EDTA at 0.5 ml/min. Cholesterol reagent (Roche Diagnostics Chol/HP 704036) at 0.16 ml/min is mixed with the column effluent through a T-connection, and the mixture is passed through a 15 m x 0.5 mm id knitted tubing reactor immersed in a 37°C water bath. The colored product produced in the presence of cholesterol is monitored in the flow stream at 505 nm, and the analog voltage from the monitor is converted to a digital signal for collection and analysis. The change in voltage corresponding to change in cholesterol concentration is plotted against time, and the area under the curve corresponding to the elution of VLDL, LDL and HDL is calculated (Perkin Elmer Turbochrome software).

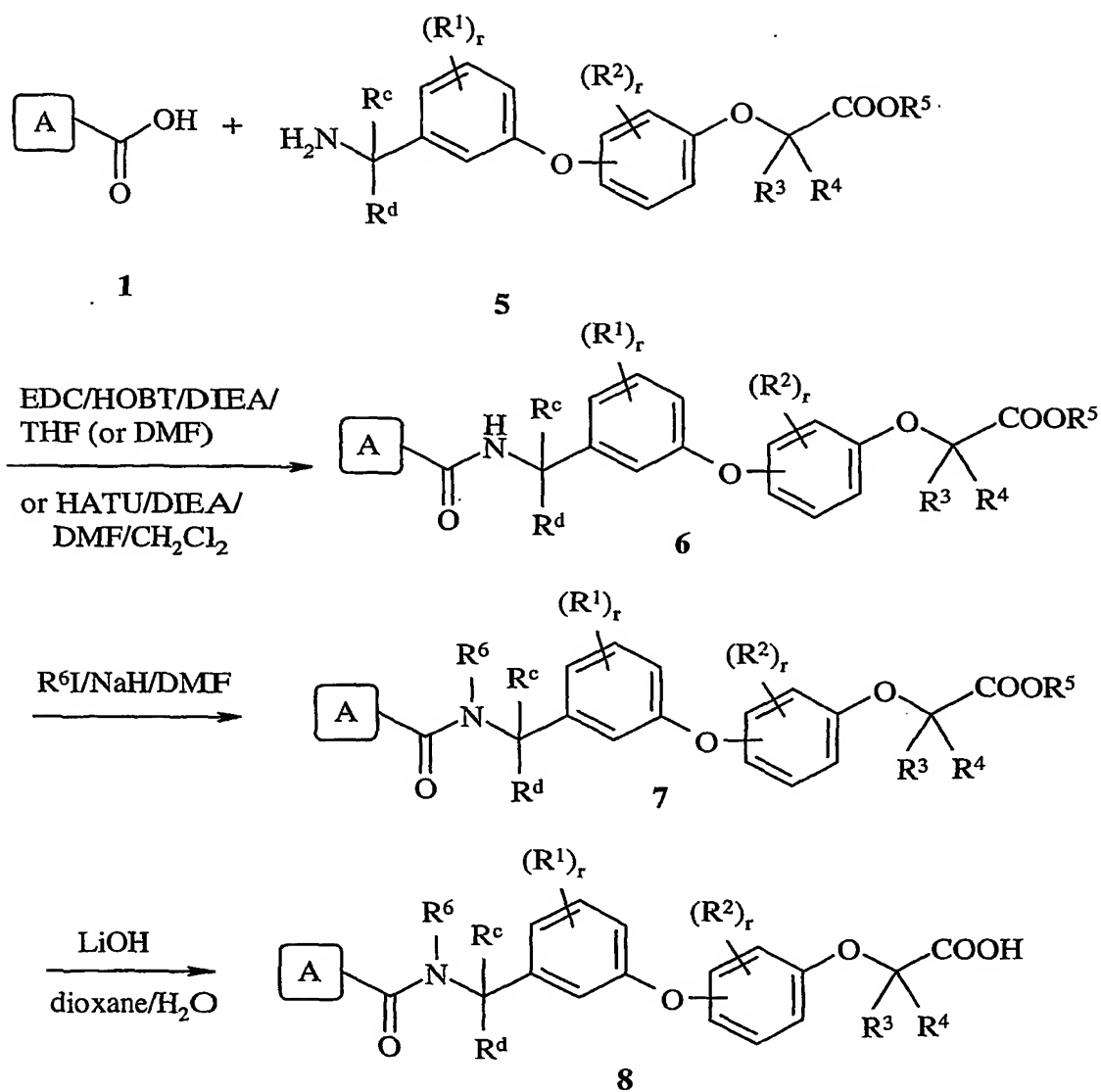
The compounds of the present invention can be prepared according to the procedures of the following schemes and examples, which may further illustrate details for the preparation of the compounds of the present invention. The compounds illustrated in the schemes and examples are, however, not to be construed as forming the only genus that is considered as the present invention.

General Reaction Scheme

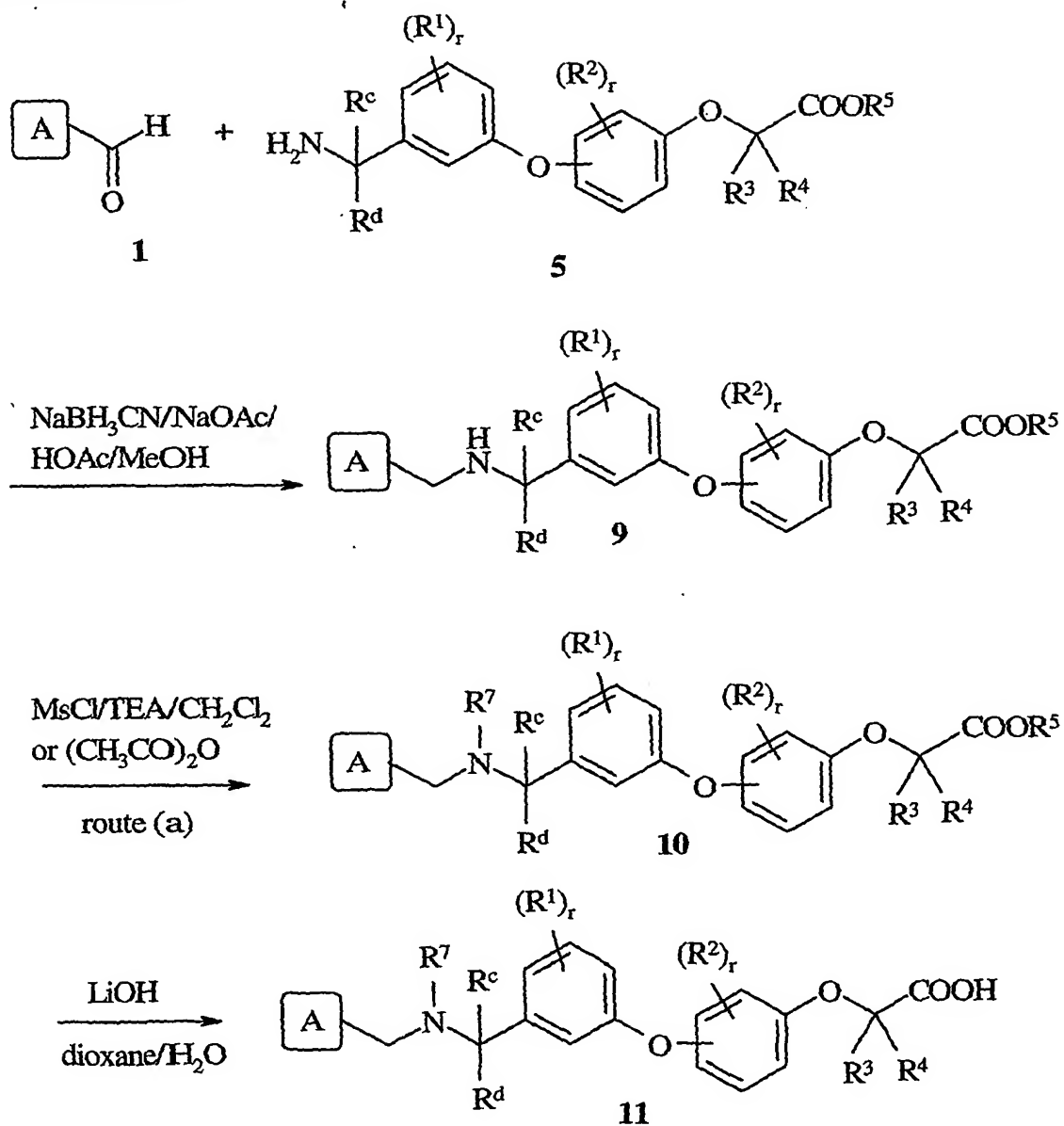
The compounds of the present invention, in general, may be prepared according to the Reaction Schemes shown below.

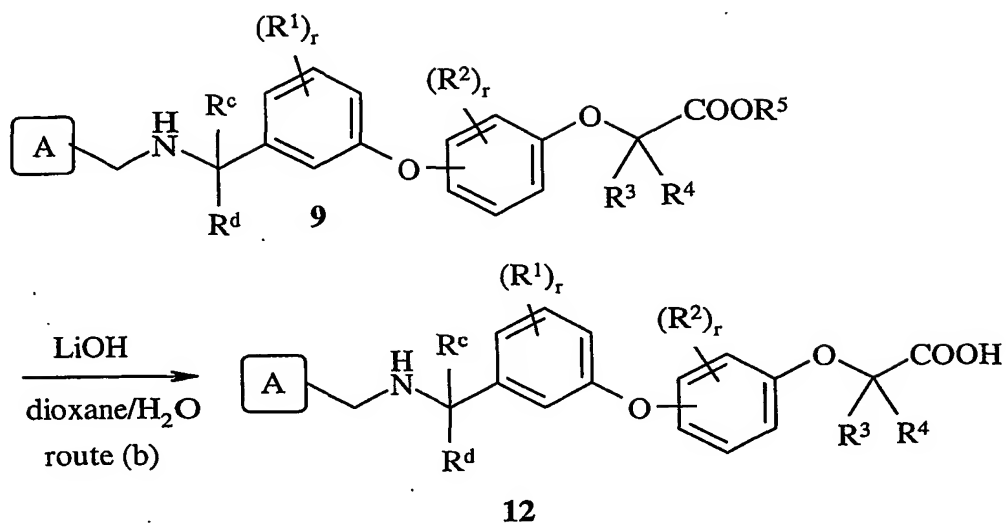
5 Reaction Scheme 1

As shown in Reaction Scheme 1, treatment of carboxylic acid 1 and amine 2 with EDC and HOBT or HATU in the presence of DIEA provides ester 3. Hydrolysis of ester under LiOH, dioxane and  $\text{H}_2\text{O}$  provides final acid 4.

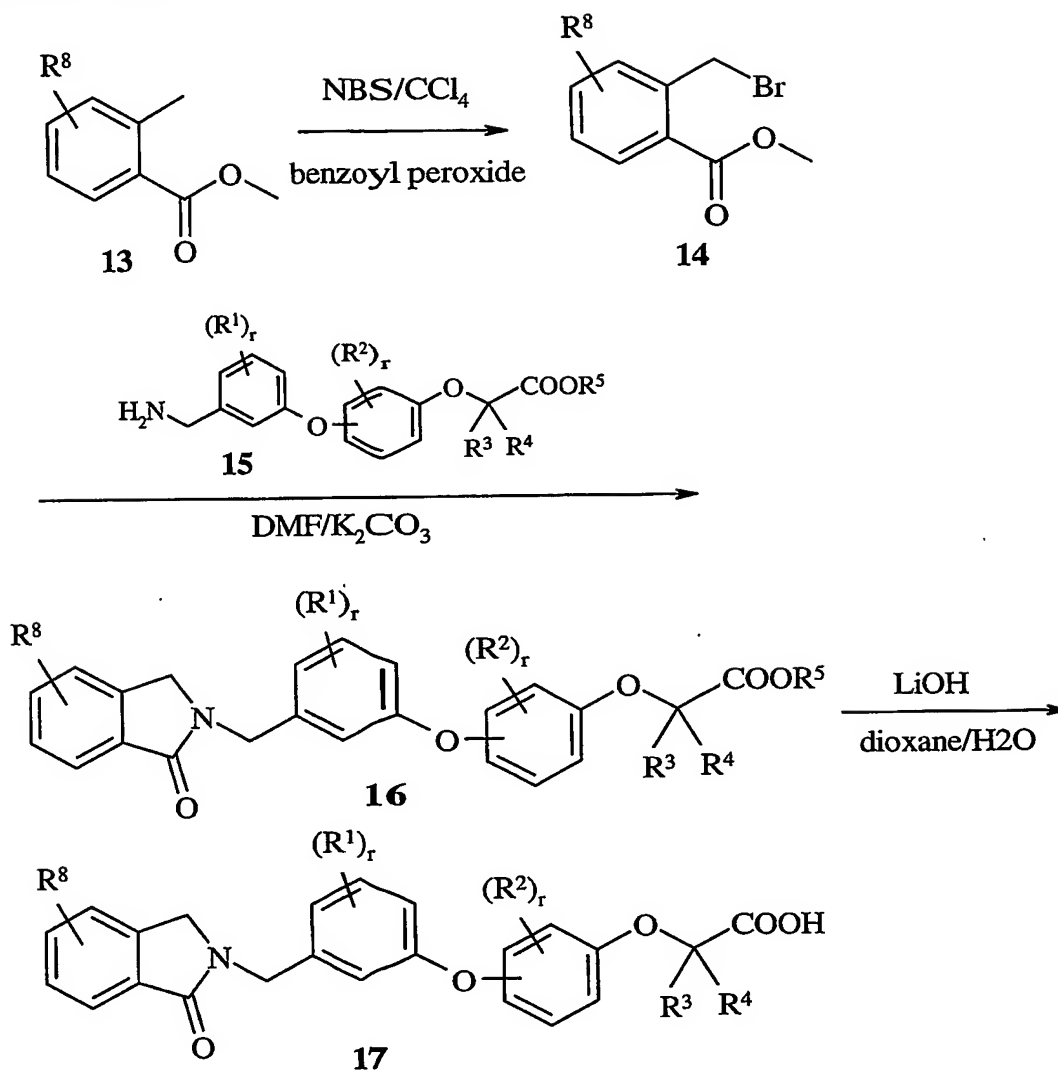
Reaction Scheme 2:

Similar to Reaction Scheme 1, treatment of carboxylic acid 1 and amine 5 with EDC and HOBT or HATU in the presence of DIEA provides ester 6 as shown in Reaction Scheme 2. Alkylation of 6 gives compound 7, which then undergoes a hydrolysis to provide final acid 8.

Reaction Scheme 3

Alternative route (b)

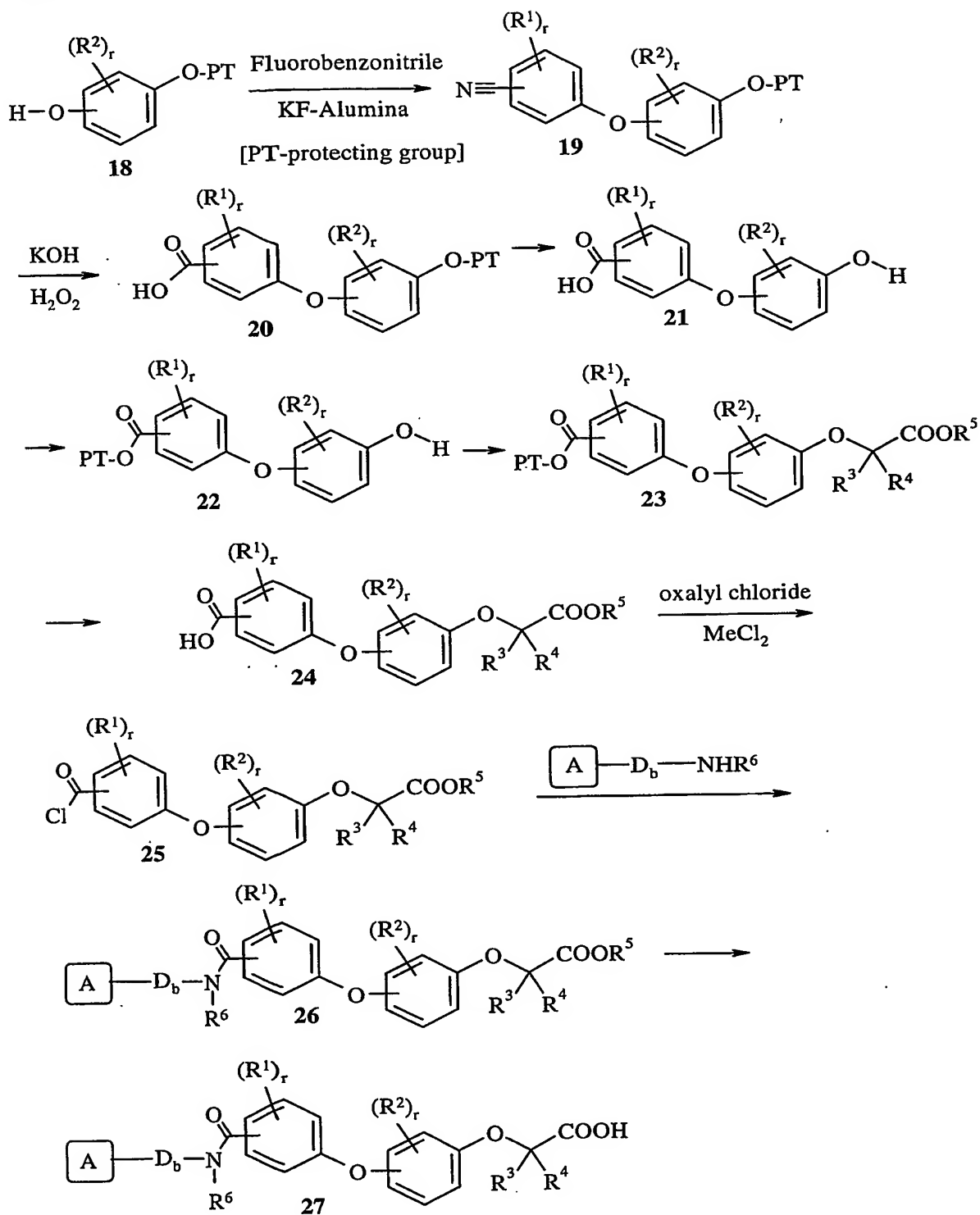
5 As shown in Reaction Scheme 3, treatment of aldehyde **1** and amine **5** with  $NaBH_3CN$  in the presence of  $NaOAc$  and  $HOAc$  provides amine **9**. Mesylation or acylation of amine **9** gives sulfonamide or amide **10**. Hydrolysis of ester under  $LiOH$ , dioxane and  $H_2O$  provides final acid **11**. Alternatively as shown in route (b), amine **9** undergoes a hydrolysis to provide final acid **12**.

Reaction Scheme 4

As shown in Reaction Scheme 4, bromination of 13 gives bromide 14.

Treatment of bromide 14 with the amine 15 under the basic condition provides lactam

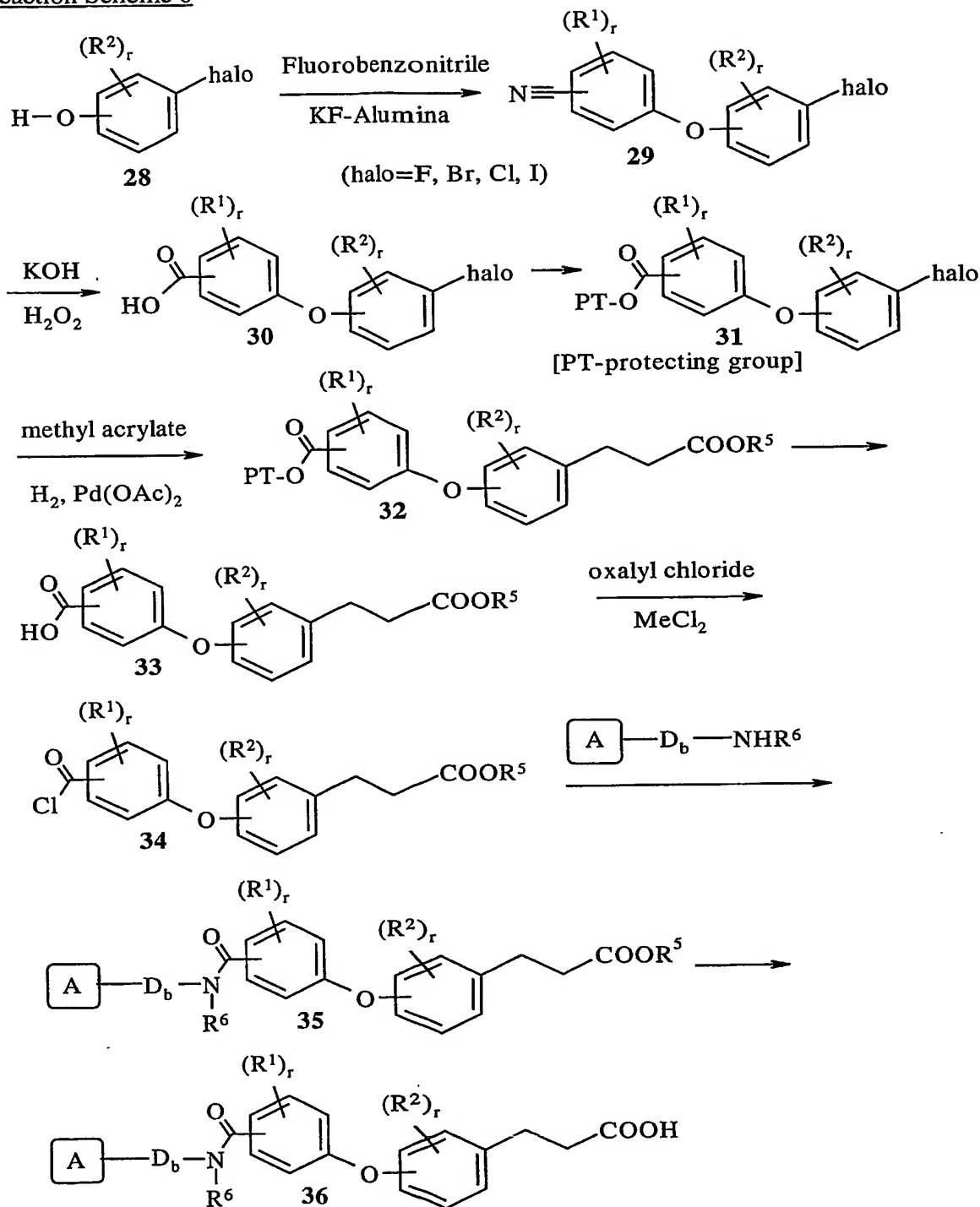
5 16, which then undergoes a hydrolysis to provide final acid 17.

Reaction Scheme 5



As shown in Reaction Scheme 5, a protected phenol **18** is reacted with fluorobenzonitrile in the presence of KF-alumina in an appropriate solvent to give the protected phenoxybenzonitrile **19**. The nitrile is hydrolyzed in a suitable condition, such as in the presence of aqueous base and hydrogen peroxide to produce the acid **20**. The protecting group (PT), such as benzyl group, is removed to give **21**. The acid is then protected with a suitable protecting group, such as benzyl group to give **22**, which is then reacted with a suitable ester-protected haloalkyl, such as ethylbromoacetate to give compound **23**. The protecting group is removed, and the acid **24** is reacted with a chlorinating agent, such as oxalyl chloride to produce compound **25**. The acid chloride compound is then reacted with an amine, such as benzylamine or cyclohexylamine in a suitable solvent, such as dichloromethane with a suitable base, such as triethylamine to give the amide ester compound **26**. The ester is cleaved using aqueous base to give the final acid compound **27**.

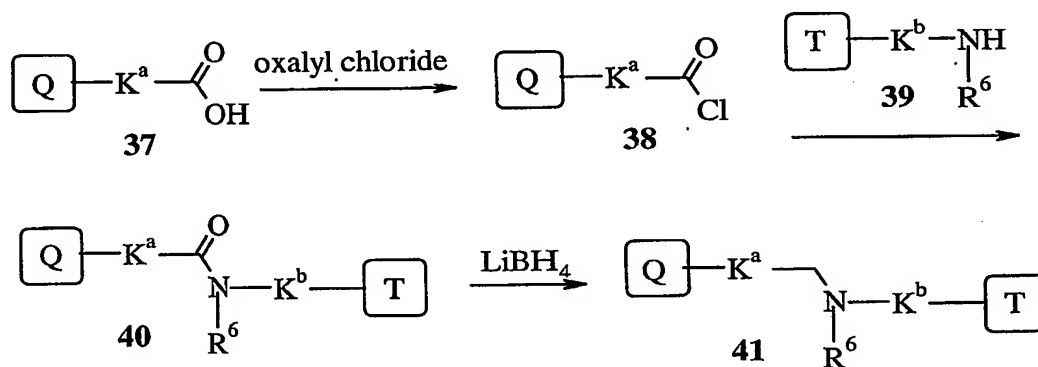
## Reaction Scheme 6



As shown in Reaction Scheme 6, a halophenol 28 is reacted with fluorobenzonitrile in the presence of KF-alumina in an appropriate solvent to give the halophenoxybenzonitrile 29. The nitrile is hydrolyzed in a suitable condition, such as in

aqueous base and hydrogen peroxide to produce the acid **30**. The acid is protected with a suitable protecting group, such as benzyl group to give **31**, which is then reacted in a palladium catalyzed Heck reaction with methyl acrylate to give the intermediate **32**. Compound **32** is reduced under standard hydrogenation condition to give the acid compound **33**. The acid is reacted with a chlorinating agent, such as oxalyl chloride to produce compound **34**. The acid chloride compound is reacted with an amine, such as benzylamine or cyclohexylamine in a suitable solvent, such as dichloromethane with a suitable base, such as triethylamine to give the amide ester **35**. The ester is cleaved using aqueous base to give the final acid product **36**.

#### Reaction Scheme 7



Q and T are each independently: aryl or alkyl;  
 $\text{R}^6$ : as defined in the specification;  
 $\text{K}^a$ : a bond,  $\text{C}_1$ - $\text{C}_{10}$  alkylene or cycloalkyl; and  
 $\text{K}^b$ :  $\text{C}_1$ - $\text{C}_{10}$  alkylene or cycloalkyl.

As shown in Reaction Scheme 7, the acid **37** is dissolved in a suitable solvent, such as dichloromethane, and treated with a chlorinating agent such as oxalyl chloride. The acid chloride **38** is then added to the amine **39** in a suitable solvent, such as dichloromethane, with a base such as triethylamine. The resulting amide **40** is then reduced using a reducing agent, such as lithium borohydride with trimethylsilyl chloride in a suitable solvent, such as tetrahydrofuran to give the final amine compound **41**.

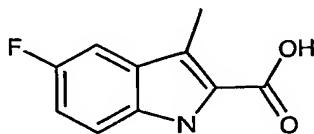
In the Schemes, Procedures and Examples below, various reagent symbols and abbreviations have the following meanings.

	ACN	Acetonitrile
	BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
5	Boc	t-butoxycarbonyl
	CBZ	benzyloxycarbonyl
	DCM	dichloromethane
	DEAD	diethyl azodicarboxylate
	DIAD	diisopropyl azodicarboxylate
10	DIPEA	diisopropylethylamine
	DMAP	4-dimethylamino pyridine
	DMF	N,N-dimethylformamide
	DMSO	dimethylsulfoxide
	eq (equiv)	equivalent(s)
15	ESI-MS	electron spray ion-mass spectroscopy
	Et	ethyl
	EtOAc	ethyl acetate
	h	hours
	HOAc	acetic acid
20	HPLC	high performance liquid chromatography
	HRMS	high resolution mass
	LRMS	low resolution mass
	LAH	lithium aluminum hydride
	Me	methyl
25	Ms	methanesulfonyl
	NBS	N-bromosuccinimide
	Pd <sub>2</sub> (dba) <sub>3</sub>	tris(dibenzylideneacetone) dipalladium(0)
	Ph	phenyl
	Pr	propyl
30	rt (r.t.)	room temperature
	TBAI	tetrabutylammonium iodide
	TBS	tertbutyldimethylsilyl
	TFA	trifluoroacetic acid
	TEA	triethylamine
35	THF	tetrahydrofuran
	TLC	thin-layer chromatography

### Preparation of Intermediates

#### Intermediate 1

#### 5-Fluoro-3-methyl-1H-indole-2-carboxylic acid



#### Step A

#### 5-Fluoro-3-methyl-1H-indole-2-carboxylic acid ethyl ester

4-Fluoroaniline (2.5 g, 22.5 mmol) is added to a solution of hydrochloric acid (5.5 mL in 9.6 mL water) and cooled to -5 °C. A solution of sodium nitrite is added dropwise (1.7 g, 24.7 mmol in 2 mL water). After the addition, reaction is stirred for 15 minutes at 0 °C, then pH is adjusted to 3-4 with sodium acetate (2.0 g, 24.3 mmol). In a separate flask, a solution of potassium hydroxide (1.4 g, 24.7 mmol in 2 mL water) is added to a solution of ethyl-2-ethylacetoacetate (3.9 g, 24.7 mmol) in ethanol (20 mL) at 0 °C followed by 28 g of ice. The diazonium solution is added immediately to the alkaline solution. The pH is adjusted to 5-6 with sodium acetate and stirred for 3 hours at 0 °C. Additional water is added and extracted 3 times with ethyl acetate, washed with brine, dried over sodium sulfate and concentrated under reduced pressure giving an oily residue. Oily residue is dissolved in a few mL ethanol and added dropwise at 78 °C to a solution of HCl in dioxane (50 mL, 4N) and HCl in ethanol (30 mL, 1N). After the addition, reaction is heated at 78 °C for approximately 2-3 hours. The reaction is cooled, then solution is concentrated under reduced pressure, water added, and extracted 3 times with dichloromethane, washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting slurry is triturated with a minimum of dichloromethane and filtered providing pure title compound (1.38 g). Recrystallization of the mother liquor material (hexane) provided additional pure product (0.68 g, 41% overall). GC/MS:  $M^+$  221;  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ).

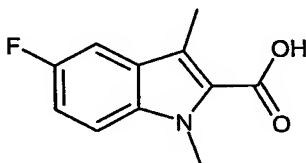
Step B

## 5-Fluoro-3-methyl-1H-indole-2-carboxylic acid

Compound of Step A (1.38 g, 6.24 mmol) is dissolved in dioxane (130 mL) and lithium hydroxide hydrate (3.9 g, 93.5 mmol), dissolved in water (65 mL), is added. Mixture is stirred at rt overnight under nitrogen, then acidified with 5 N HCl. Water is added and extracted with EtOAc, washed with brine, dried over sodium sulfate and concentrated under reduced pressure to give the title compound (0.76 g, 63%). Mass (ES): 192 (M-H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Intermediate 2

## 5-Fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid

Step A

## 5-Fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid ethyl ester

To a suspension of 60% sodium hydride (162 mg, 4.1 mmol) in dry DMF (10 mL), cooled to 0 °C under nitrogen, is added dropwise the compound from Step A of Example 1 (600 mg, 2.7 mmol), dissolved in DMF (2 mL). The mixture is stirred at 0 °C for 45 minutes, then iodomethane (0.26 mL, 4.1 mmol) is added dropwise. Bath is removed after 1 hour and stirring is continued overnight. Reaction is quenched with ice water and a precipitate formed, which is filtered and dried providing title compound (600. mg, 94%) that is utilized without further purification. GC/MS: M<sup>+</sup> 235; <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>).

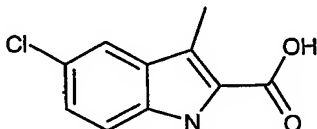
Step B

## 5-Fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid

The title compound is prepared according to Step B of Intermediate 1, utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid ethyl ester. Mass (ES): 206 (M-H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Intermediate 3

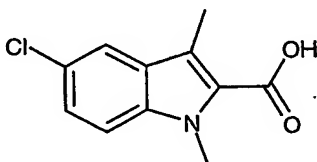
## 5-Chloro-3-methyl-1H-indole-2-carboxylic acid



The title compound is prepared according to Intermediate 1 utilizing 4-chloroaniline and ethyl-2-ethylacetoacetate. Mass (ES<sup>-</sup>): 208 (M-H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Intermediate 4

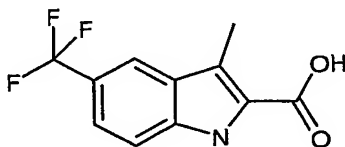
## 5-Chloro-1,3-dimethyl-1H-indole-2-carboxylic acid



The title compound is prepared according to Intermediate 2 utilizing 5-chloro-3-methyl-1H-indole-2-carboxylic acid ethyl ester (Intermediate 3, Step A) and iodomethane. Mass (ES<sup>-</sup>): 222 (M-H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Intermediate 5

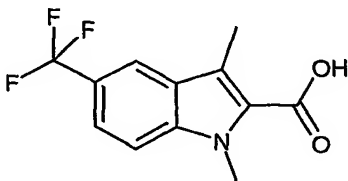
## 3-Methyl-5-trifluoromethyl-1H-indole-2-carboxylic acid



The title compound is prepared according to Intermediate 1 utilizing 4-trifluoromethylaniline and ethyl-2-ethylacetoacetate. Mass (ES<sup>-</sup>): 242 (M-H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Intermediate 6

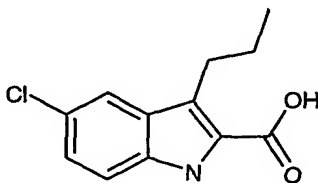
1,3-Dimethyl-5-trifluoromethyl-1H-indole-2-carboxylic acid



5 The title compound is prepared according to Intermediate 2 utilizing 1,3-dimethyl-5-trifluoromethyl-1H-indole-2-carboxylic acid ethyl ester (Intermediate 5, Step A) and iodomethane. Mass ( $ES^-$ ): 256 ( $M-H^+$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Intermediate 7

5-Chloro-3-propyl-1H-indole-2-carboxylic acid

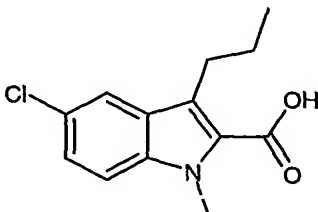


10

The title compound is prepared according to Intermediate 1 utilizing 4-chloroaniline and ethyl-2-n-butylacetoacetate. Mass ( $ES^-$ ): 236 ( $M-H^+$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Intermediate 8

5-Chloro-1-methyl-3-propyl-1H-indole-2-carboxylic acid



15

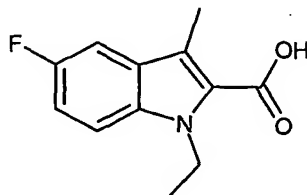
The title compound is prepared according to Intermediate 2 utilizing 5-chloro-3-propyl-1H-indole-2-carboxylic acid ethyl ester (Intermediate 7, Step A) and iodomethane. Mass ( $ES^-$ ): 250 ( $M-H^+$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

20



Intermediate 9

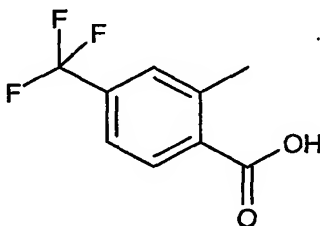
1-Ethyl-5-fluoro-3-methyl-1H-indole-2-carboxylic acid



The title compound is prepared according to Intermediate 2 utilizing  
5 5-fluoro-3-methyl-1H-indole-2-carboxylic acid ethyl ester (Intermediate 1, Step A) and  
iodoethane. Mass ( $ES^-$ ): 250 ( $M-H^+$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Intermediate 10

2-Methyl-4-(trifluoromethyl)-benzoic acid

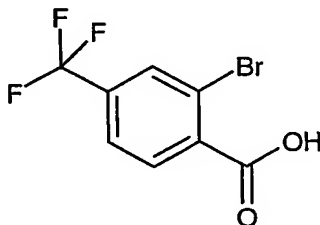


10

The compound of *N,N,N,N*-tetramethylethylenediamine (19.8 mL, 131.9 mmol) is added to dry THF (120 mL) under nitrogen and cooled to  $-78^\circ C$  with a dry ice acetone bath. Sec-butyl lithium (94 mL, 131.9 mmol, 1.4 M in cyclohexane) is added dropwise keeping the temperature between  $-78^\circ C$  to  $-70^\circ C$  with overhead stirring.  
15 Suspension is stirred 15 minutes, then 4-(trifluoromethyl)-benzoic acid (11.4 g, 59.8 mmol) dissolved in 70 mL THF is added dropwise within the above temperature range and allowed to warm to  $-50^\circ C$  to  $-40^\circ C$ . Stirring is continued for 2 hours within that temperature range. Mixture is cooled to  $-78^\circ C$  and iodomethane (14.9 mL, 239.2 mmol) is added in 2-3 minutes. Bath is removed after 10 minutes and the reaction is stirred  
20 overnight. Reaction is quenched with water, extracted with ether, and the aqueous layer acidified with 5N HCl. Acidified solution is extracted with ether, washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography, eluting with 10 % EtOAc in hexane then 25 % EtOAc in hexane provides the title compound (2.4 g, 20 %). Mass ( $ES^-$ ): 203  $^1HNMR$  (400 MHz,  $CDCl_3$ ).

Intermediate 11

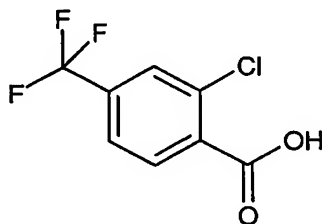
## 2-Bromo-4-trifluoromethyl-benzoic acid



Anhydrous copper (II) bromide (1.34 g, 6.0 mmol) and *t*-butyl nitrite  
5 (90%) (0.86 g, 7.5 mmol) are added to dry acetonitrile (20 mL) under nitrogen and the  
reaction is heated to 65 °C. 2-Amino-4-trifluoromethyl-benzoic acid (1.03 g, 5.0 mmol)  
is added in 3 portions and stirred for 15 minutes. Reaction is cooled and 5 N HCl is  
added, extracted with ether, washed with brine, dried over sodium sulfate and  
concentrated under reduced pressure. Purification by flash chromatography, eluting with  
10 15 % EtOAc in hexane then 25 % EtOAc in hexane provides the title compound (0.80 g,  
60 %). Mass (ES<sup>-</sup>): 267; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Intermediate 12

## 2-Chloro-4-trifluoromethyl-benzoic acid



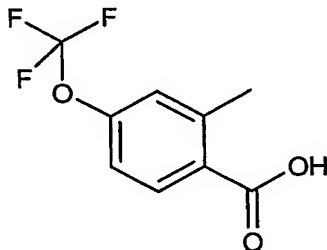
15

The title compound is prepared according to Intermediate 11 utilizing 2-  
amino-4-trifluoromethyl-benzoic acid and copper (II) chloride. Mass (ES<sup>-</sup>): 223 (M-H<sup>+</sup>);  
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

20

Intermediate 13

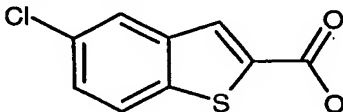
2-Methyl-4-trifluoromethoxybenzoic acid



The title compound is prepared according to Intermediate 10 utilizing 4-trifluoromethoxy-benzoic acid. Mass ( $ES^-$ ): 219 ( $M-H^+$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Intermediate 14

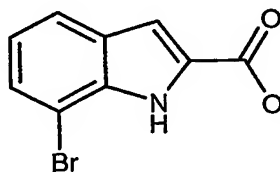
5-Chloro-benzo[b]thiophene-2-carboxylic acid



The title compound is prepared according to Intermediate 1, Step B, utilizing 5-chloro-benzo[b]thiophene-2-carboxylic acid methyl ester. Mass ( $ES^-$ ): 211 ( $M-H^+$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Intermediate 15

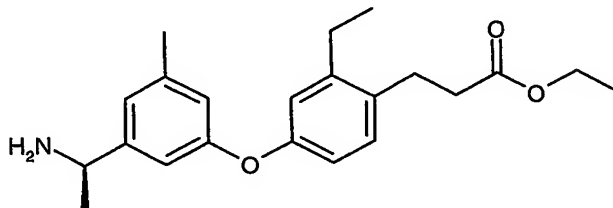
7-Bromo-1H-indole-2-carboxylic acid



The title compound is prepared according to Intermediate 1, Step B, utilizing 7-bromo-1H-indole-2-carboxylic acid ethyl ester. Mass ( $ES^-$ ): 238 ( $M-H^+$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Intermediate 16

3-{4-[3-(1-Amino-ethyl)-5-methyl-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester

Step A

5        3-[4-(3-Bromo-5-methyl-phenoxy)-2-ethyl-phenyl]-propionic acid ethyl ester

The compounds of 3,5-dibromotoluene (13.5 g, 54.0 mmol), 3-(2-ethyl-4-hydroxy-phenyl)-propionic acid ethyl ester (3.0 g, 13.5 mmol) (Intermediate 59), cesium carbonate (5.27 g, 16.2 mmol), copper (I) chloride (0.67 g, 6.7 mmol), and 2,2,6,6-tetramethyl-3,5-heptanedione (0.62 g, 3.4 mmol) are added to 1-methyl-2-pyrrolidinone (35 ml) and  
10        heated overnight at 120 °C under nitrogen. After cooling, HCl acid (50 mL, 1N) is added to quench the reaction. Additional water is added and extracted 3 times with ethyl ether, washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography, eluting with 5 % EtOAc in hexane then 10 % EtOAc in hexane provides the title compound (2.7 g, 51 %). MS(ES<sup>+</sup>): 410 (M+NH<sub>4</sub><sup>+</sup>);  
15        <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>).

Step B

3-[4-(3-Acetyl-5-methyl-phenoxy)-2-ethyl-phenyl]-propionic acid ethyl ester

The compound from Step A (2.7 g, 6.9 mmol), is dissolved in toluene (85 mL), and tributyl(1-ethoxyvinyl)tin (2.56 mL, 7.6 mmol) and

20        dichlorobis(triphenylphosphine)palladium(II) (0.48 g, 0.69 mmol) are added. The solution is degassed and heated at 100 °C under nitrogen for 5 hours. After the reaction is cool, HCl acid (40 mL, 1N) is added and stirred for 1 hour. Reaction mixture is filtered through Celite and washed with EtOAc. Organic layer is separated, washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Oil is dissolved in  
25        ethyl ether (300 mL) and an aqueous solution of KF (200 mL, 0.1N) is added. Mixture is stirred overnight. Precipitate is removed by filtration, washed with ethyl ether, and the organic layer removed. The water layer is extracted twice with ethyl ether, then the

ethers layers are combined, washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography, eluting with 5 % EtOAc in hexane then 10 % EtOAc in hexane provides the title compound (1.3 g, 52 %). MS(ES<sup>+</sup>): 372 (M+NH<sub>4</sub><sup>+</sup>); <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>).

5

Step C

3-{2-Ethyl-4-[3-(1-hydroxy-ethyl)-5-methyl-phenoxy]-phenyl}-propionic acid ethyl ester (R)-2-methyl-CBS-oxazaborolidine (0.34 mL, 0.36 mmol, 1N in toluene) is dissolved in dry toluene (3.5 mL) and borane-*N,N*-diethylaniline complex (0.64 mL, 3.6 mmol) is added. Flask is immersed in a water bath and the compound from Step B (1.3 g, 3.6 mmol) is dissolved in toluene (9.0 mL) and is added dropwise to the solution keeping the temperature between 19 °C and 23 °C. Reaction is stirred 45 minutes under nitrogen. Reaction is quenched with methanol (1.2 mL), followed by 1N HCl (2.2 mL) and stirred for 15 minutes. Aqueous layer is separated, extracted twice with ethyl acetate. Organic layers are combined, washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography, eluting with 10 % EtOAc in hexane then 20 % EtOAc in hexane provides the title compound (1.1 g, 85 %). MS(ES<sup>+</sup>): 374 (M+NH<sub>4</sub><sup>+</sup>); <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>).

10

15

Step D

3-{4-[3-(1-Azido-ethyl)-5-methyl-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester Compound from Step C (1.1 g, 3.1 mmol) and diphenylphosphoryl azide (0.81 mL, 3.8 mmol) are dissolved in toluene (10.0 mL), cooled to 0 °C, and DBU is added dropwise. Reaction is stirred 2 hours under nitrogen at 0 °C, then at rt overnight. Azidotrimethylsilane (0.41 mL, 3.1 mmol) and tetrabutylammonium fluoride (1M in THF, 3.1 mL, 3.1 mmol) are added to the solution and heated at 40 °C for 8 hours. Solvent is removed under reduced pressure. Purification by flash chromatography, eluting with 10 % EtOAc in hexane then 15 % EtOAc in hexane provides the title compound (0.93 g, 78 %). MS(ES<sup>+</sup>): 399 (M+NH<sub>4</sub><sup>+</sup>); <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>).

20

25

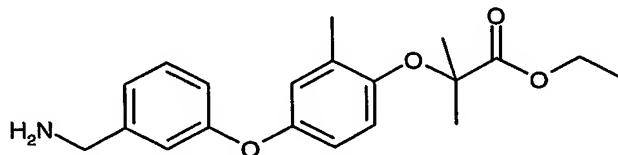
Step E

3-{4-[3-(1-Amino-ethyl)-5-methyl-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester

Compound from Step D (0.93 g, 2.3 mmol) and triphenylphosphine (0.96 g, 3.8 mmol) are stirred overnight in THF (20 mL) and water (2 mL). Solvent is removed under reduced pressure with bath at rt, extracted into ethyl acetate, washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by SCX column, eluting with 10 % ammonia (2.0 M in methanol) in dichloromethane provides the title compound (0.93 g, 78 %). MS(ES<sup>+</sup>): 399 (M+NH<sub>4</sub><sup>+</sup>); <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>).

Intermediate 17

2-[4-(3-Aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester

Step A

2-[4-(3-Cyano-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester

The compounds of 2-(4-hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid ethyl ester (4.5 g, 18.9 mmol) (WO 20030721) 3-cyanophenylboronic acid (5.5 g, 37.8 mmol), dried copper (II) acetate (6.8 g, 37.8 mmol), and dried molecular sieve (11.3 g) are added to dichloromethane (225 ml). Pyridine (15.3 mL, 189.0 mmol) is added dropwise at rt. Reaction is stirred overnight with a drying tube in place. Reaction mixture is filtered through Celite and washed with dichloromethane. Filtrate is concentrated under reduced pressure. Purification by flash chromatography, eluting with 10 % EtOAc in hexane then 15 % EtOAc in hexane provides the title compound (3.0 g, 47 %). MS(ES<sup>+</sup>): 340 (M+H<sup>+</sup>); <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>).

Step B

2-[4-(3-Aminomethyl)-phenoxy]-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester

Compound from Step A (3.0 g, 8.9 mmol) is reacted overnight in a Parr shaker with 5 % Pd/C (0.3 g) in glacial acetic acid (422 mL) at rt with 40 psi hydrogen. Reaction mixture is filtered, most of acetic acid removed under reduced pressure with rt bath. Ethyl acetate is added to oily residue. Solution is washed with diluted sodium

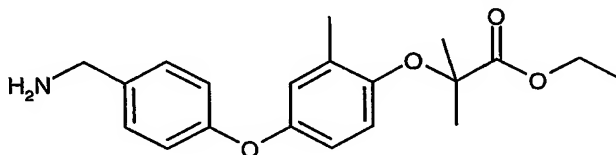
bicarbonate, washed with brine, dried over sodium sulfate and concentrated under reduced pressure providing the title compound (2.8 g, 92 %) that is utilized without purification.

MS( $ES^+$ ): 343 ( $M+H^+$ );  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

5

Intermediate 18

2-[4-(4-Aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester

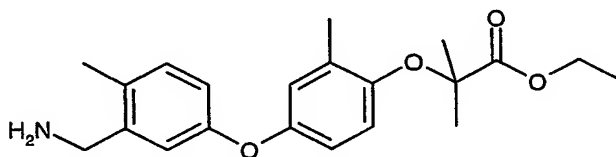


The title compound is prepared according to Intermediate 17 utilizing 4-cyanophenylboronic acid and 2-(4-hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid ethyl ester (WO 2003072102). Mass ( $ES^+$ ): 366 ( $M+Na^+$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Intermediate 19

2-[4-(3-Aminomethyl-4-methyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester



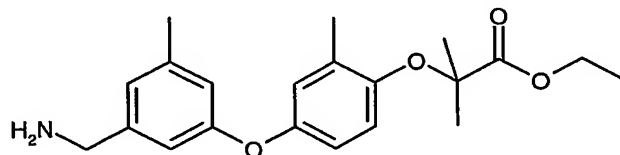
15

2-[4-(3-Cyano-4-methyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (240. mg, 0.68 mmol) (Intermediate 51) is reacted overnight in a Parr shaker with Raney nickel (0.2 g) in ammonia (2N solution in methyl alcohol, 50 mL) at 40 °C with 60 psi hydrogen. Reaction mixture is filtered and concentrated under reduced pressure with rt bath providing the title compound (245 g, quantitative) that is utilized without purification. MS( $ES^+$ ): 358 ( $M+H^+$ );  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

20

Intermediate 20

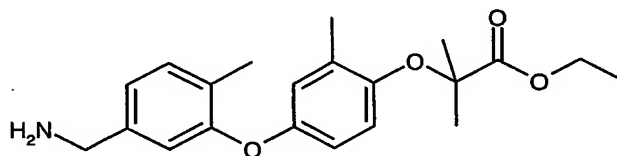
2-[4-(3-Aminomethyl-5-methyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester



- 5            The title compound is prepared according to Intermediate 19 utilizing 2-[4-(3-cyano-5-methyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 55). Mass ( $ES^+$ ): 358 ( $M+H^+$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Intermediate 21

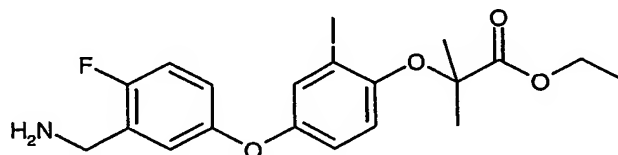
- 10        2-[4-(5-Aminomethyl-2-methyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester



- The title compound is prepared according to Intermediate 19 utilizing 2-[4-(5-cyano-2-methyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 54). Mass ( $ES^+$ ): 358 ( $M+H^+$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ ).
- 15

Intermediate 22

2-[4-(3-Aminomethyl-4-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester



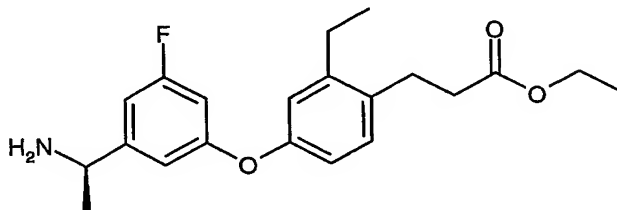
20

- The title compound is prepared according to Intermediate 19 utilizing 2-[4-(3-cyano-4-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 53). Mass ( $ES^+$ ): 362 ( $M+H^+$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ ).



Intermediate 23

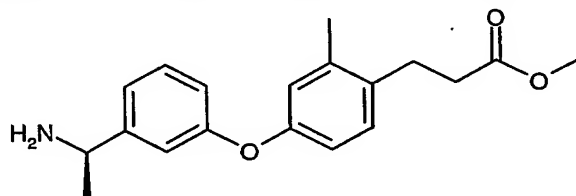
3-{4-[3-(1-Amino-ethyl)-5-fluoro-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester



5 The title compound is prepared according to Intermediate 16 utilizing 1,3-dibromo-5-fluoro-benzene and 3-(2-ethyl-4-hydroxy-phenyl)-propionic acid ethyl ester (Intermediate 59). Mass ( $ES^+$ ): 360 ( $M+H^+$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Intermediate 24

3-{4-[3-(1-Amino-ethyl)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester



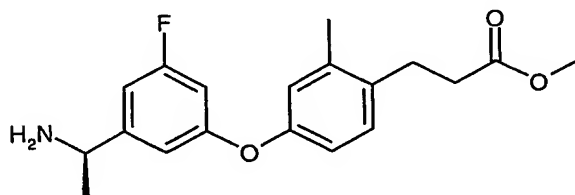
10

The title compound is prepared according to Intermediate 16, Steps A, C, D, and E utilizing 3'-bromoacetophenone and 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (*J.Chem.Soc.Perkin Trans.1*; 4; 1990; 1041-1045). Mass ( $ES^+$ ): 314 ( $M+H^+$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

15

Intermediate 25

3-{4-[3-(1-Amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester



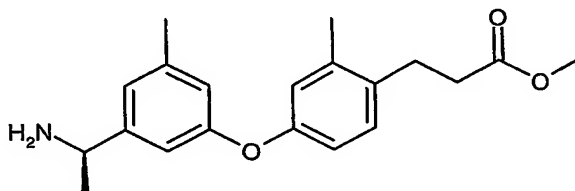
20

The title compound is prepared according to Intermediate 16 utilizing 1,3-dibromo-5-fluoro-benzene and 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl

ester (*J.Chem.Soc.Perkin Trans.1*; 4; 1990; 1041-1045). Mass ( $ES^+$ ): 332 ( $M+H^+$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

#### Intermediate 26

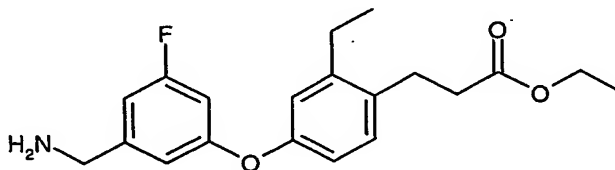
- 5     3-{4-[3-(1-Amino-ethyl)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester



The title compound is prepared according to Intermediate 16 utilizing 3,5-dibromotoluene and 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester  
10 (*J.Chem.Soc.Perkin Trans.1*; 4; 1990; 1041-1045). Mass ( $ES^+$ ): 328 ( $M+H^+$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

#### Intermediate 27

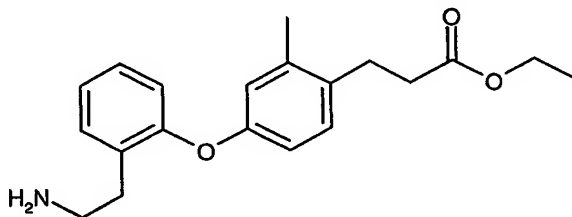
- 15     3-[4-(3-Aminomethyl-5-fluoro-phenoxy)-2-ethyl-phenyl]-propionic acid ethyl ester



The title compound is prepared according to Intermediate 33 utilizing 3,5-difluorobenzonitrile and 3-(2-ethyl-4-hydroxy-phenyl)-propionic acid ethyl ester (Intermediate 59). Mass ( $ES^+$ ): 360 ( $M+H^+$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Intermediate 28

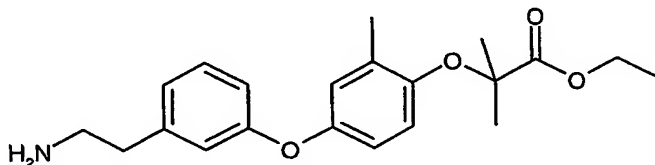
3-{4-[2-(2-Amino-ethyl)-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester



5 3-{4-[2-(2-tert-Butoxycarbonylamino-ethyl)-phenoxy]-2-methyl-phenyl}-  
propionic acid ethyl ester (600 mg, 1.4 mmol) (Intermediate 56) is dissolved in dioxane (5  
mL) and cooled with an ice bath. Cooled HCl in dioxane (30 mL, 4N) is added and  
reaction is stirred for 1.5 hours, and then concentrated under reduced pressure. Oil is  
purified through an SCX column eluting with 10 % ammonia (2N in methanol) in  
dichloromethane providing the title compound (390 mg, 85 %). Mass (ES<sup>+</sup>): 328  
10 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Intermediate 29

2-{4-[3-(2-Amino-ethyl)-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl  
ester

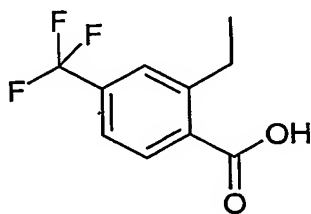


15 The title compound is prepared according to Intermediate 28 utilizing 2-  
{4-[3-(2-tert-butoxycarbonylamino-ethyl)-phenoxy]-2-methyl-phenoxy}-2-methyl-  
propionic acid ethyl ester (Intermediate 58). Mass (ES<sup>+</sup>): 358 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400  
MHz, CDCl<sub>3</sub>).

20

Intermediate 30

## 2-Ethyl-4-trifluoromethyl-benzoic acid

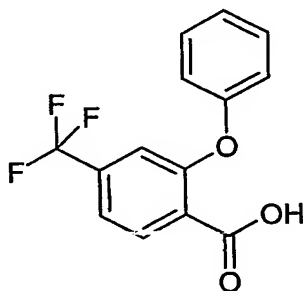


2-Methyl-4-trifluoromethyl-benzoic acid (0.10 g, 0.49 mmol) is dissolved  
5 in THF (8 ml), and the solution is cooled to  $-78^{\circ}\text{C}$ . LDA (2.0 M in  
heptane/THF/ethylbenzene, 0.55 mL, 1.1 mmol) is added. The mixture is warmed to  $-35^{\circ}\text{C}$ . After the dark purple color disappeared, the mixture is cooled back to  $-78^{\circ}\text{C}$  and  
LDA (2.0 M in heptane/THF/ethylbenzene, 0.55 mL, 1.1 mmol) is added, stirred at  $-35^{\circ}\text{C}$   
10 for 1h. The reaction mixture is cooled back to  $-78^{\circ}\text{C}$  and MeI (0.15 ml, 2.4 mmol) is  
added, warmed to RT and stirred overnight. The mixture is concentrated, acidified with  
5M HCl, extracted with EtOAc, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ . Removal of  
solvents give a residue (0.20 g) as a mixture of 56 % the title compound and 44 % of the  
starting material. This mixture is used without isolation and the purification is done after  
peptide coupling. Mass ( $\text{ES}^+$ ): 217 ( $\text{M}-\text{H}^+$ );  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ).

15

Intermediate 31

## 2-Phenoxy-4-trifluoromethyl-benzoic acid

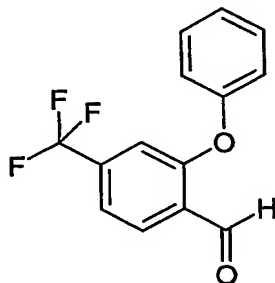


A mixture of 2-fluoro-4-(trifluoromethyl) benzoic acid (2.50 g, 12 mmol),  
20 phenol (2.26 g, 24 mmol) and  $\text{Cs}_2\text{CO}_3$  (11.73g, 36 mmol) in DMF (20 ml) is heated at  
 $100^{\circ}\text{C}$  under  $\text{N}_2$  overnight. The mixture is cooled to RT, quenched with  $\text{H}_2\text{O}$ , acidified  
with 5 M HCl, extracted with EtOAc, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and

concentrated. Purification by reversed phase HPLC provides the title compound. Mass ( $ES^-$ ): 281.3 ( $M-H^+$ );  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

### Intermediate 32

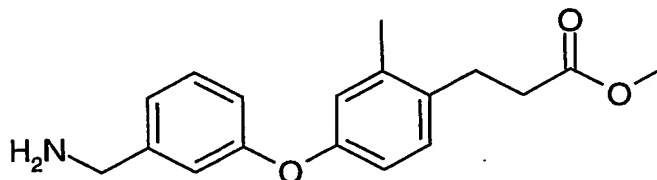
#### 2-Phenoxy-4-(trifluoromethyl)-benzaldehyde



A mixture of 2-fluoro-4-(trifluoromethyl)benzaldehyde (4.97g, 26 mmol), phenol (2.64g, 28 mmol) and  $Cs_2CO_3$  (16.94g, 26 mmol) in DMF (20 ml) is heated at 85 °C under  $N_2$  overnight. The reaction mixture is cooled to RT. Water is added, extracted with EtOAc, washed with brine, dried over  $Na_2SO_4$ , filtered and concentrated. Purification by chromatography, eluting with 5% EtOAc in hexane then 15% EtOAc in hexane provides the title compound (5.30g). Mass ( $ES^-$ ): 265.3 ( $M-H^+$ );  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

### Intermediate 33

#### 3-[4-(3-Aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



#### Step A

#### 3-[4-(3-Cyano-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester

A mixture of 3-fluorobenzonitrile (4.82 ml, 45 mmol), 3-(4-Hydroxy-2-methyl-phenyl)-propionic acid methyl ester (*J.Chem.Soc.Perkin Trans.1*; 4; 1990; 1041-1045) (8.74g, 45 mmol) and  $Cs_2CO_3$  (29.32g, 90 mmol) in DMF (60 ml) is heated at 100 °C under  $N_2$  overnight. The reaction mixture is cooled to RT, quenched with ice- $H_2O$ ,

extracted with EtOAc, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. Purification by chromatography, eluting with 10% EtOAc in hexane then 15% EtOAc in hexane provides the title compound (8.56g). MS: ( $\text{ES}^+$ ) 296.1 ( $\text{M}+\text{H}^+$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ).

5

Step B

3-[4-(3-Aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester

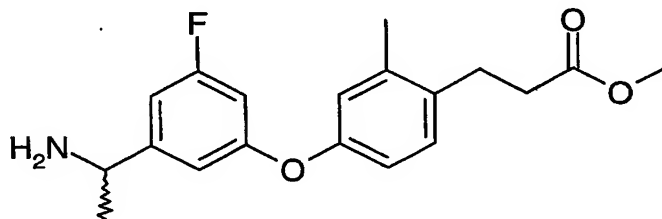
The compound from Step A (6.16g, 21mmol) is dissolved in HOAc (75 ml). 5% Pd/C (0.62g) is added. The mixture is hydrogenated at RT under 40 – 60 Psi overnight. The reaction mixture is filtered, concentrated, dissolved in EtOAc, washed with dilute  $\text{NaHCO}_3$  and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated again to provide the title compound (5.97g). MS: ( $\text{ES}^+$ ) 300.2 ( $\text{M}+\text{H}^+$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ).

10

Intermediate 34

15

3-{4-[3-(1-Amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester

Step A

3-[4-(3-Bromo-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester

20

The title compound is prepared as described in Intermediate 16, Step A utilizing 1,3-Dibromo-5-fluoro-benzene and 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (J.Chem.Soc.Perkin Trans.1; 4; 1990; 1041-1045). MS: ( $\text{ES}^+$ ) 385 ( $\text{M}+\text{NH}_4^+$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ).

Step B

3-[4-(3-Acetyl-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester

The title compound is prepared as described in Intermediate 16, Step B utilizing the compound Step A above. MS:(ES<sup>+</sup>) 331(M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Step C

3-{4-[3-Fluoro-5-(1-hydroxyamino-ethyl)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester

The compound from Step B (0.54 g, 1.64 mmol) is dissolved in EtOH (8 ml). NH<sub>2</sub>OH·HCl (0.11 g, 1.64 mmol), NaOAc (0.27 g, 3.28 mmol) and H<sub>2</sub>O are added, heated under reflux for 1h. The reaction mixture is concentrated. Water is added, extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated again to provide the title compound (0.56g). MS: (ES<sup>+</sup>) 346.2 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

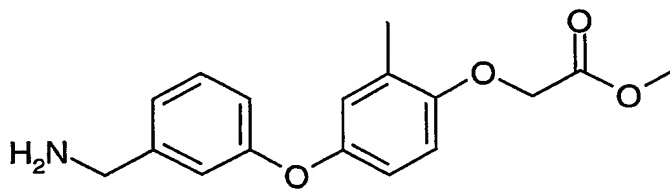
Step D

3-{4-[3-(1-Amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester

The compound from Step C (0.56g, 1.62 mmol) is dissolved in a mixture of MeOH (9.0 ml), AcOH (9.0 ml) and H<sub>2</sub>O (4.4 ml). Zn dust (0.42g, 6.49 mmol) is added, stirred at RT for 6 h. The reaction mixture is filtered, concentrated. The residue is dissolved in EtOAc, washed with dilute NaHCO<sub>3</sub>, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated again to provide the title compound (0.53g). MS: (ES<sup>+</sup>) 332.1 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Intermediate 35

[4-(3-Aminomethyl-phenoxy)-2-methyl-phenoxy]-acetic acid methyl ester

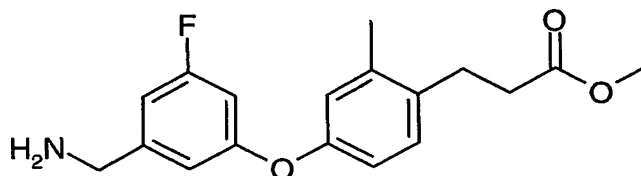


The title compound is prepared according to the procedure described in Intermediate 33 utilizing 3-fluoro-benzonitrile and (4-hydroxy-2-methyl-phenoxy)-acetic acid methyl ester. MS:(ES<sup>+</sup>) 302.1 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

5

Intermediate 36

3-[4-(3-Aminomethyl-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester

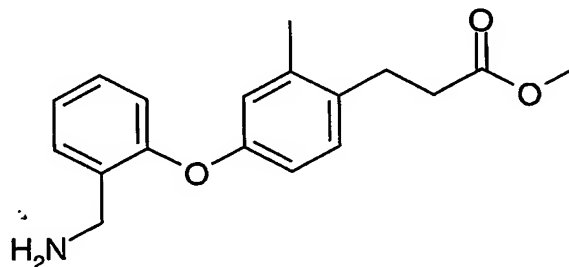


10

The title compound is prepared according to the procedure described in Intermediate 33 utilizing 3,5-difluoro-benzonitrile and 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (*J.Chem.Soc.Perkin Trans.1*; 4; 1990; 1041-1045). MS: (ES<sup>+</sup>) 318.2 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Intermediate 37

3-[4-(2-Aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



15

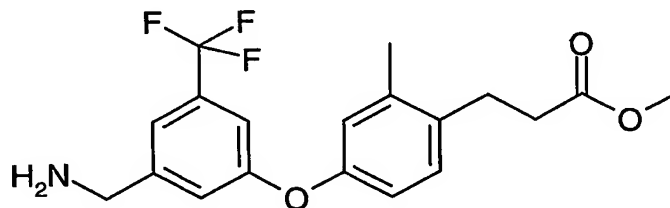
The title compound is prepared according to the procedure described in Intermediate 33 utilizing 2-fluoro-benzonitrile and 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (*J.Chem.Soc.Perkin Trans.1*; 4; 1990; 1041-1045). MS: (ES<sup>+</sup>) 300.12 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

20



Intermediate 38

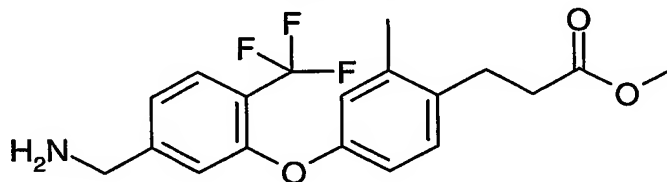
3-[4-(3-Aminomethyl-5-trifluoromethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



5 The title compound is prepared according to the procedure described in Intermediate 33 utilizing 3-fluoro-5-trifluoromethyl-benzonitrile and 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (*J.Chem.Soc.Perkin Trans.1*; 4; 1990; 1041-1045). MS: (ES<sup>+</sup>) 368.1 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Intermediate 39

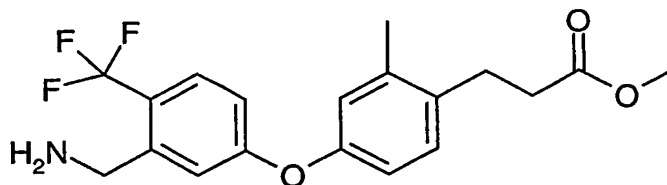
10 3-[4-(5-Aminomethyl-2-trifluoromethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



15 The title compound is prepared according to the procedure described in Intermediate 33 utilizing 3-fluoro-4-trifluoromethyl-benzonitrile and 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (*J.Chem.Soc.Perkin Trans.1*; 4; 1990; 1041-1045). MS: (ES<sup>+</sup>) 368.1 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Intermediate 40

20 3-[4-(3-Aminomethyl-4-trifluoromethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



Step A

3-[4-(3-Cyano-4-trifluoromethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester

The title compound is prepared according to the procedure described in Intermediate 33, Step A, utilizing 5-fluoro-2-trifluoromethyl-benzonitrile and 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (*J.Chem.Soc.Perkin Trans.1*; 4; 1990; 1041-1045). MS: (ES<sup>+</sup>) 363.9.1 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

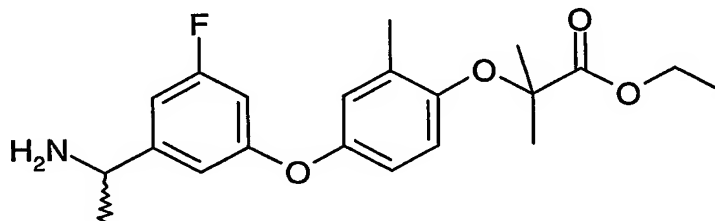
Step B

3-[4-(3-Aminomethyl-4-trifluoromethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester

The compound from Step A (0.35 g, 0.96 mmol) is dissolved in 2 M NH<sub>3</sub> in MeOH (50 ml). Raney Nickel (0.2 g) is added. The mixture is hydrogenated at 40 °C under 60 Psi overnight. The reaction mixture is filtered and concentrated to provide the crude title compound (0.44g). MS: (ES<sup>+</sup>) 368.06 (M+H<sup>+</sup>).

Intermediate 41

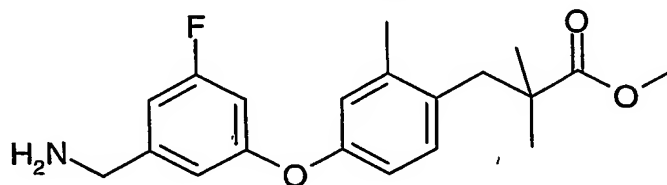
2-{4-[3-(1-Amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl ester



The title compound is prepared according to the procedure described in Intermediate 34 utilizing 1,3-dibromo-5-fluoro-benzene and 2-(4-hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid ethyl ester (WO 2003072102). MS: (ES<sup>+</sup>) 376.2 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Intermediate 42

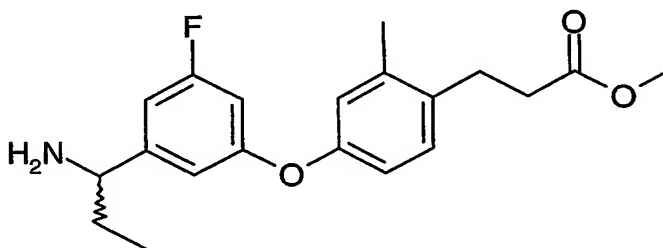
3-[4-(3-Aminomethyl-5-fluoro-phenoxy)-2-methyl-phenyl]-2,2-dimethyl-propionic acid methyl ester



The title compound is prepared according to the procedure described in Intermediate 33 utilizing 3,5-difluoro-benzonitrile and 3-(4-hydroxy-2-methyl-phenyl)-2,2-dimethyl-propionic acid methyl ester (Intermediate 60). MS: (ES<sup>+</sup>) 346.2 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Intermediate 43

3-{4-[3-(1-Amino-propyl)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester

Step A

3-[4-(3-Fluoro-5-propionyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester

The title compound is prepared according to the procedure described in Intermediate 33, Step A utilizing 3,5-difluoropropiophenone and 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (*J.Chem.Soc.Perkin Trans.1*; 4; 1990; 1041-1045). MS: (ES<sup>+</sup>) 345.2 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Step B

3-{4-[3-Fluoro-5-(1-hydroxyamino-propyl)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester

The title compound is prepared according to the procedure described in Intermediate 34, Step C utilizing the compound from Step A. MS: (ES<sup>+</sup>) 360.2 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Step C

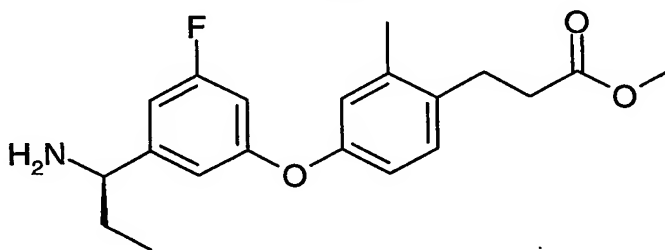
5     3-{4-[3-(1-Amino-propyl)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester

The title compound is prepared according to the procedure described in Intermediate 34, Step D utilizing the compound from Step B. MS: (ES<sup>+</sup>) 346.3 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

10

Intermediate 44

3-{4-[3-(1-Amino-propyl)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester



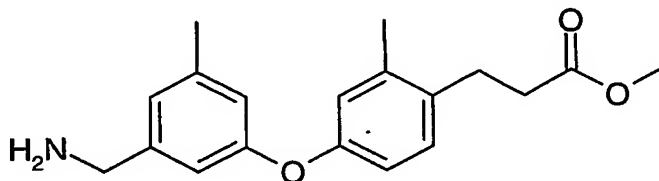
15

The title compound is prepared according to the procedure described in Intermediate 16 utilizing 3-[4-(3-fluoro-5-propionyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 43, Step A). Chiral HPLC t<sub>R</sub> = 6.532 min (LC column: CHIRALPAK AD; 4.6 x 250 mm; 100% MeOH with 0.2 % DMEA; flow rate: 1.0 ml/min); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

20

Intermediate 45

3-[4-(3-Aminomethyl-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



Step A

3-[4-(3-Bromo-5-cyano-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester

The title compound is prepared according to the procedure described in Intermediate 16, Step A utilizing 3,5-dibromo-benzonitrile and 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (*J. Chem. Soc. Perkin Trans. 1*, 4, 1990, 1041-1045). MS: (ES<sup>+</sup>) 393.2 (M+NH<sub>4</sub><sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Step B

3-[4-(3-Cyano-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester

The compound from Step A above (0.60 g, 1.6 mmol) is dissolved in DMF (10 ml). Trimethylboroxine (0.22 ml, 1.6 mmol), (Ph<sub>3</sub>P)<sub>4</sub>Pd (0.18 g, 0.16 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.66 g) are added. The reaction mixture is heated at 115 °C under N<sub>2</sub> overnight. The reaction mixture is filtered through Celite, washed with EtOAc. The filtrate is concentrated. The residue is purified by chromatography, eluting with 10% EtOAc in hexane then 15% EtOAc in hexane providing the title compound (0.40 g). MS: (ES<sup>327.5</sup>) (M+NH<sub>4</sub><sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

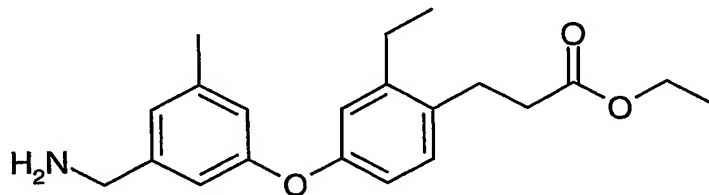
Step C

3-[4-(3-Aminomethyl-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester

The title compound is prepared according to the procedure described in Intermediate 33, Step B utilizing the compound from Step B above. The crude product is purified by SCX column eluting with 10 % 2M NH<sub>3</sub> in MeOH /CH<sub>2</sub>Cl<sub>2</sub>. MS: (ES<sup>+</sup>) 314.5 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Intermediate 46

3-[4-(3-Aminomethyl-5-methyl-phenoxy)-2-ethyl-phenyl]-propionic acid ethyl ester

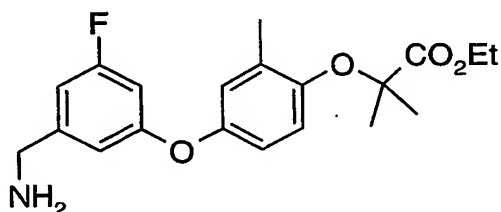


The title compound is prepared according to the procedure described in Intermediate 45 utilizing 3,5-dibromo-benzonitrile and 3-(2-ethyl-4-hydroxy-phenyl)-

propionic acid ethyl ester (Intermediate 59). MS: (ES<sup>+</sup>) 342.5 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

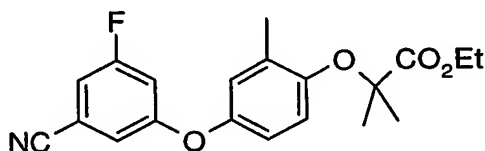
Intermediate 47

- 5      2-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester



Step A

- 2-[4-(3-cyano-5-fluorophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester



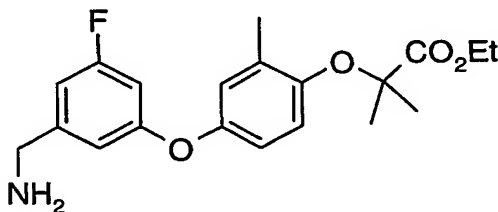
10

3,5-difluorobenzonitrile (1.286 g, 9.24 mmol) is added to a suspension of KF/Al<sub>2</sub>O<sub>3</sub> (5.0 g, 40% KF), 18-crown-6 (220 mg, 0.84 mmol) and compound (a) from Intermediate 55, Step A (2.0 g, 8.4 mmol) in CH<sub>3</sub>CN (150 mL, HPLC grade). The mixture is warmed to reflux. After 2 h, the reaction is allowed to reach r.t., filtered through

15 Celite and washed with EtOAc/brine. The organic layer is dried, filtered and concentrated, and the crude residue is flash chromatographed on SiO<sub>2</sub> (5-10% EtOAc/hexanes), affording 1.95 g of the title compound (65%, white solid).

Step B

- 20      2-[4-(3-methylamino-5-fluorophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester

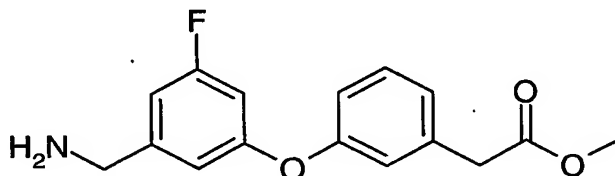


Pd/C (140 mg, 10% Pd on activated C, 0.027 mmol) is added to a solution of compound obtained from Step A (1.70 g, 4.927 mmol) in glacial AcOH (200 mL). The mixture is stirred at r.t. under H<sub>2</sub> atmosphere (40 psi) overnight (c.a. 14 h) and filtered through Celite (CH<sub>2</sub>Cl<sub>2</sub> washings). The AcOH is neutralized with NaHCO<sub>3</sub>, and the mixture partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The organic layer is dried, filtered and concentrated. The crude residue is flash chromatographed on SiO<sub>2</sub> (0.2% ethyldimethylamine, 30% iPrOH, 70% hexane) to afford about 1.35 g of the title compound (79%, colorless oil).

10

Intermediate 48

[3-(3-Aminomethyl-5-fluoro-phenoxy)-phenyl]-acetic acid methyl ester

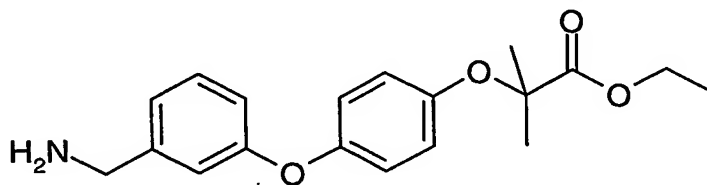


15

The title compound is prepared according to the procedure described in Intermediate 33 utilizing 3,5- difluoro-benzonitrile and (3-hydroxy-phenyl)-acetic acid methyl ester (WO 2003072102). MS: (ES<sup>+</sup>) 290.3 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Intermediate 49

2-[4-(3-Aminomethyl-phenoxy)-phenoxy]-2-methyl-propionic acid ethyl ester



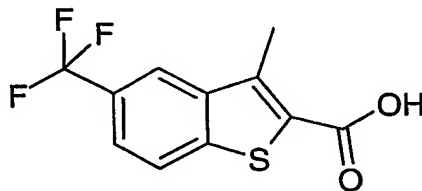
20

The title compound is prepared according to the procedure described in Intermediate 40 utilizing 3-fluorobenzonitrile and 2-(4-hydroxy-phenoxy)-2-methyl-propionic acid ethyl ester (WO 2002081454) except that the reaction is carried out at rt and 500 Psi for Step B. MS: (ES<sup>+</sup>) 330.3 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

25

Intermediate 50

## 3-Methyl-5-trifluoromethyl-benzo[b]thiophene-2-carboxylic acid

Step A

## 1-(2-Methylsulfanyl-5-trifluoromethyl-phenyl)-ethanone

A solution of 2-fluoro-5-trifluoromethyl acetophenone (3.0 g, 14.5 mmol) in dry DMF (20 mL) was treated with sodium thiomethoxide (1.22 g, 17.4 mmol) and the reaction was stirred for 2 hours at rt under N<sub>2</sub>. The reaction was quenched with 1 N HCl (10 mL), diluted with Et<sub>2</sub>O and then extracted twice with water. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed *in vacuo* to afford crude product that was absorbed on silica gel and then column purified using 5/1 hexanes/acetone to afford 2.88 g (85%) of the product. R<sub>f</sub> = 0.57 (1/1 hexanes/acetone). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.05 (s, 1H), 7.69 (d, 1H, J = 8.31 Hz), 7.42 (d, 1H, J = 8.80 Hz), 2.68 (s, 3H), 2.48 (s, 3H).

Step B

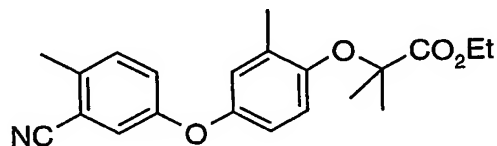
## 3-Methyl-5-trifluoromethyl-benzo[b]thiophene-2-carboxylic acid

A mixture of 1-(2-methylsulfanyl-5-trifluoromethyl-phenyl)-ethanone (made above) (2.06 g, 8.79 mmol) and bromoacetic acid (7.33 g, 52.8 mmol) in acetic acid (20 mL) was heated to reflux and stirred for 20 hours under N<sub>2</sub>. The reaction was cooled and water was added to form a slurry. The slurry was filtered and the solids rinsed with water to afford 1.59 g (69%) of the product after drying in a vacuum oven at 45 °C. R<sub>f</sub> = 0.18 (1/1 hexanes/acetone). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>). MS (ES<sup>-</sup>) *m/z* mass calcd for C<sub>11</sub>H<sub>7</sub>O<sub>2</sub>SF<sub>3</sub> 260, found 259 (M - 1, 100%).

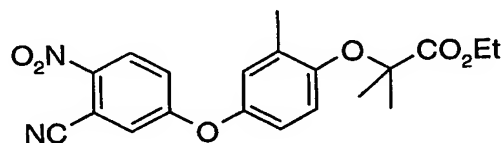


Intermediate 51

2-[4-(3-cyano-4-methylphenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester

Step A

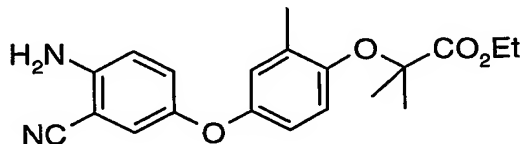
5 2-[4-(3-cyano-4-nitrophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester



A mixture of 9.6 g (58 mmol) of 2,5-difluorobenzonitrile, 13.8 g (58 mmol) of 2-(4-hydroxy-2-methylphenoxy)-2-methylpropionic acid ethyl ester (WO 2003072102), 34.5 g of 40% w/w potassium fluoride-alumina, 1.56 g (5.8 mmol) of 18-crown-6 in CH<sub>3</sub>CN is refluxed under argon atmosphere. After 1 hour, the reaction mixture is cooled to rt, partitioned between equal parts of ether and water, and shaken vigorously. The aqueous layer and alumina sediments are separated and the resulting organic phase is washed once with a saturated potassium chloride solution. The organic phase is dried over MgSO<sub>4</sub>, and concentrated in vacuo. The crude is used in the next step without further purification. About 19.6 g of 2-[4-(3-cyano-4-nitrophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester are obtained.

Step B

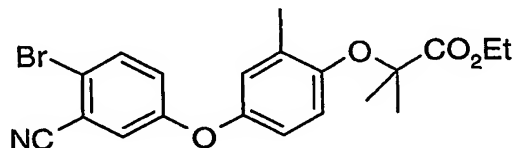
2-[4-(4-amino-3-cyanophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester



20 A mixture of 7 g (18.2 mmol) of 2-[4-(3-cyano-4-nitrophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester, 700 mg of Pd(C) 10% in 50 ml of EtOH is hydrogenated for two hours at rt. The mixture is filtered over celite and washed with EtOH. The solvent is evaporated to give 6.4 g of the title compound, which is used for the next step without further purification.

## Step C

2-[4-(4-bromo-3-cyanophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester



To a mixture of 2.5 ml (21.2 mmol) of <sup>t</sup>BuONO and 3.79 g (17 mmol) of  
5 CuBr<sub>2</sub> in acetonitrile at 65°C under argon atmosphere is added 5 g (14.1 mmol) of 2-[4-(4-  
amino-3-cyanophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester in 10 ml  
of acetonitrile. After the addition is washed, the reaction is stirred at the same  
temperature for 15 min. The reaction is allowed to reach rt, and HCl (2N) is added. The  
mixture is extracted with ether (3x20 ml). The organic phase is washed with HCl (2N),  
10 dried over MgSO<sub>4</sub> and concentrated to give 5.8 g of the title compound, which is used  
for the next step without further purification.

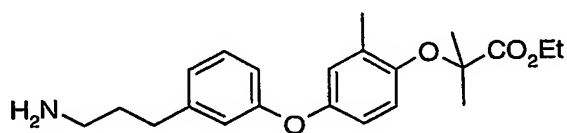
## Step D

2-[4-(3-cyano-4-methylphenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester

A sealed tube is charged with 3 g (7.2 mmol) of 2-[4-(4-bromo-3-  
15 cyanophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester, 80 mg (0.35  
mmol) of Pd(OAc)<sub>2</sub>, 192 mg (0.7 mmol) of P(o-tolyl)<sub>3</sub>, 1.1 ml (7.9 mmol) Sn(CH<sub>3</sub>)<sub>4</sub> and  
3 ml of Et<sub>3</sub>N in 5 ml of DMF and is heated at 115°C under argon atmosphere overnight.  
To the mixture, HCl (2N) is added (10ml), and the mixture is extracted with ether (3x50  
ml). The organic phase is dried over MgSO<sub>4</sub> and concentrated. The desired product is  
20 purified by silica gel chromatography using hexane/ethyl acetate 15:1 as eluent to  
obtain 680 mg (27%) of the title compound. MS Data (Ion Trap): m/z 353.8 [M+H] as  
base peak, m/z 376.1 [M+Na] and m/z 511.7.

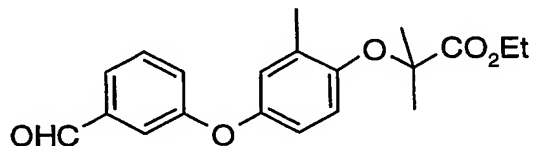
## Intermediate 52

25 2-{4-[3-(3-amino-propyl)-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl  
ester



Step A

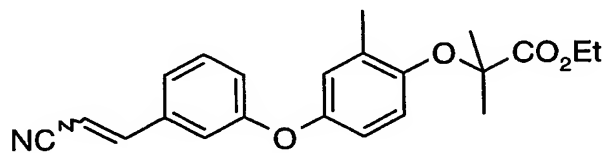
2-[4-(3-formilphenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester



A sealed tube is charged with Pd(OAc)<sub>2</sub> (36 mg, 0.14 mmol), 2-  
 5 (ditertbutylphosphino)biphenyl (76 mg, 0.4 mmol) and K<sub>3</sub>PO<sub>4</sub> (3.56 g, 14 mmol). The  
 tube is evacuated and back-filled with argon and fitted with a rubber septum. Toluene (10  
 ml) followed by 3-bromo benzaldehyde (0.81 ml, 7 mmol) and 2-(4-hydroxy-2-  
 methylphenoxy)-2-methylpropionic acid ethyl ester (WO 2003072102) (2 g, 8.4 mmol) in  
 10 toluene (10 ml) are added via syringe. The tube is sealed under argon and stirred at 110  
 °C for two days. The mixture is diluted with 30 ml of diethyl ether, filtered through a pad  
 of celite and concentrated to leave a crude oil. The resulting oil is purified by flash  
 chromatography on silica gel using 10:1 hexanes/ethyl acetate as eluent to obtain 900 mg  
 of the title compound.

Step B

15 2-{4-[3-(2-cyanovinyl)-phenoxy]-2-methylphenoxy}-2-methylpropionic acid ethyl ester



Z:E mixture

To a solution of diethyl-(cyanomethyl)-phosphonate (0.466 ml, 2.63mmol)  
 in THF (5 ml) at -78°C is added dropwise <sup>t</sup>BuOK (2.63 ml, 2.63 mmol) under a nitrogen  
 blanket. The solution is stirred for 30 min., and 2-[4-(3-formilphenoxy)-2-  
 20 methylphenoxy]-2-methylpropionic acid ethyl ester (900 mg, 2.63 mmol) in THF (10 ml)  
 is added slowly at the same temperature. The mixture is stirred at -78°C for another 30  
 min. and then warmed to 0°C, quenched with 25% NH<sub>4</sub>Cl (aq), extracted with EtOAc,  
 washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated. Purification: silica gel  
 chromatography. Eluent 12:1 hexanes/ethyl acetate affords 825 mg of a mixture 70:30 of  
 25 E/Z isomers of the title compound.

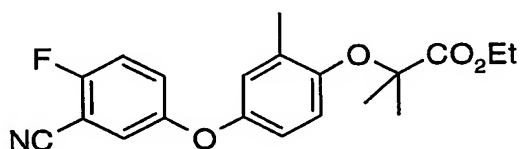
Step C

2-{4-[3-(3-amino-propyl)-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl ester

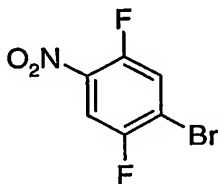
A mixture of 2-{4-[3-(2-cyanovinyl)-phenoxy]-2-methylphenoxy}-2-methypropionic acid ethyl ester (700 mg, 1.9 mmol) and 70 mg of Pd(C) 10% in 10ml of EtOH is hydrogenated one hour at rt. Then, it is filtered over celite and washed with EtOH. The solvent is evaporated, and the crude is purified using silica gel chromatography, 25:1 hexane/ethyl acetate as eluent to give 460 mg of the title compound. MS Data (Ion Trap): m/z 390 [M+Na] as base peak, m/z 368 [M+H], m/z 294 and 254 (in positive mode).

Intermediate 53

2-[4-(3-cyano-4-fluorophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester

Step A

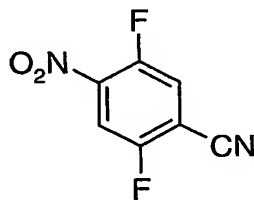
1-bromo-2,5-difluoro-4-nitrobenzene



To a solution of 2-bromo-1,4-difluorobenzene (10 g, 51.8 mmol) in 40 ml of sulfuric acid at 0°C is added dropwise 35 ml of nitric acid while maintaining an internal temperature below 20°C. The mixture is then poured into ice and extracted with ether (3x100 ml). The organic phase is washed with NaHCO<sub>3</sub> (3 times), dried over MgSO<sub>4</sub> and evaporated. The crude is purified by silica gel chromatography (hexane/acetone 10:1) to afford 11.25 g of the title compound.

Step B

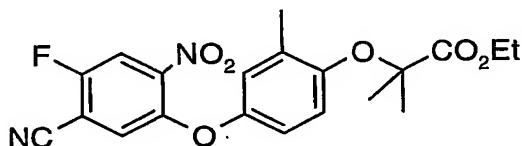
2,5-difluoro-4-nitrobenzonitrile



A mixture of 1-bromo-2,5-difluoro-4-nitrobenzene (5g, 21 mmol) and 2.44 g (27 mmol) of CuCN in 20 ml of DMF is heated at 160°C in a sealed tube, under argon atmosphere overnight. The mixture is washed with 50 ml of water and NH<sub>4</sub>OH (3x20 ml) and then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100ml). The organic phase is dried over MgSO<sub>4</sub> and evaporated to give 3.8 g of the title compound, which is used in next step without further purification.

Step C

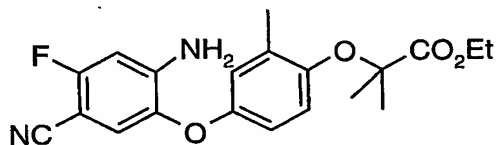
2-[4-(5-cyano-4-fluoro-2-nitrophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester



A mixture of 2,5-difluoro-4-nitrobenzonitrile (1.6 g, 8.7 mmol), 2.1 g (8.7 mmol) of 2-(4-hydroxy-2-methylphenoxy)-2-methylpropionic acid ethyl ester (WO 2003072102), 5.25 g of 40% w/w potassium fluoride-alumina, 230 mg (0.87 mmol) of 18-crown-6 in CH<sub>3</sub>CN is refluxed under argon atmosphere. After 1 hour, the mixture is cooled to rt, partitioned between equal parts of ether and water, and shaken vigorously. The aqueous layer and alumina sediments are separated, and the resulting organic phase is washed once with a saturated potassium chloride solution. The organic phase is dried over MgSO<sub>4</sub> and concentrated in vacuo. The crude is purified by silica gel chromatography (hexane/ethyl acetate 15:1) to yield 2.4 g of the title compound.

Step D

2-[4-(2-amino-5-cyano-4-fluorophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester



A mixture of 2-[4-(5-cyano-4-fluoro-2-nitrophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester (1.5 g, 3.7 mmol), 150 mg of Pd(c) 10% in 30 ml of EtOH is hydrogenated overnight at rt. Then, it is filtered over celite and washed with EtOH. The solvent is evaporated to give 1.4 g of the title compound, which is used for the next step without further purification.

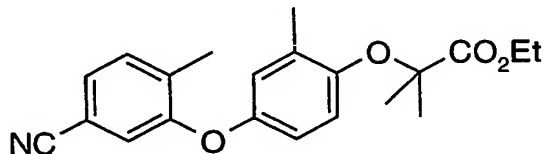
Step E

2-[4-(3-cyano-4-fluorophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester

To a solution of 2-[4-(2-amino-5-cyano-4-fluorophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester (1.4 g, 3.7 mmol) in a mixture of 80ml THF/ 8 ml water is added 2.91 ml (52.6 mmol) of  $\text{H}_3\text{PO}_2$ , catalytic amount of  $\text{Cu}_2\text{O}$  and a solution of 312 mg (4.5 mmol) of  $\text{NaNO}_2$  in 3 ml of water. After stirring at rt overnight, the mixture is diluted with an aqueous  $\text{NaHCO}_3$  solution and extracted with ethyl acetate (3x100 ml). The combined organic extracts are washed with aqueous  $\text{NH}_4\text{Cl}$ , dried over  $\text{MgSO}_4$  and evaporated to dryness. Purification by silica gel chromatography (hexane/ethyl acetate 10:1) provides about 479 mg of the title compound. MS Data: (ion trap/ESI +): m/z 380.1  $[\text{M}+\text{Na}]$  as base peak and m/z 358.1  $[\text{M}+\text{H}]$ .

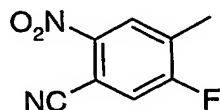
Intermediate 54

2-[4-(5-cyano-2-methylphenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester



Step A

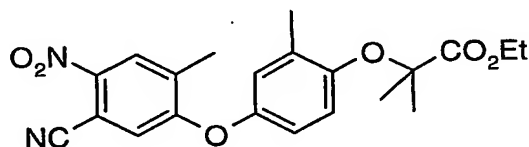
## 3-fluoro-4-methyl-5-nitrobenzonitrile



- Add potassium nitrate (4.51 g, 44.54 mmol) in three or four portions to 3-fluoro-4-methylbenzonitrile (6.02 g, 44.54 mmol) in concentrated  $\text{H}_2\text{SO}_4$  (50 ml) at  $0^\circ\text{C}$  and stir. Stir the deep orange solution for 2 hours at  $0^\circ\text{C}$  and then for 1 hour at rt. Add the mixture over 800 ml of ice and extract with 150 ml of AcOEt. Allow the mixture to warm at rt and separate the organic layer. Extract again the aqueous layer with 100 ml of AcOEt. Combine the organic extracts and washed with water (50 ml) and brine (50 ml). Dry the organic layer over magnesium sulfate, filter, and concentrate under reduced pressure to give the crude product (7.64 g, 93% yield). Although the product can be used without further purification, flash chromatogapy can be performed in silica using hexane:ethyl acetate (10:1) as eluent.

Step B

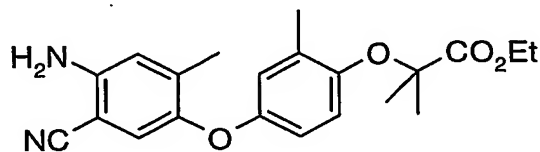
- 2-[4-(5-cyano-4-nitro-2-methylphenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester



- Prepare a solution of 3-fluoro-4-methyl-5-nitrobenzonitrile (2.85 g, 15.49 mmol) and ethyl 2,2-dimethyl-2-(3'-methyl-4'-hydroxy)phenoxyacetate (WO 2003072102) (3.69 g, 15.49 mmol) in 150 ml of acetonitrile, and add 7.12 g of potassium fluoride (40% in alumina) and 18-crown-6 ether (409 mg, 1.55 mmol) and heat to reflux for 2 hours. Cool the mixture at rt, and add equal parts of water and diethyl ether (80 ml + 80 ml). Separate the aqueous layer and the alumina sediments and wash the organic layer with water (20 ml) and brine (20 ml). Dry the organic layer with sodium sulfate, filter and concentrate under reduced pressure to give the crude product (5.77 g, 94 %), which can be used without further purification.

Step C

2-[4-(5-cyano-4-amino-2-methylphenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester



- 5 Prepare a solution of compound obtained from Step B (5.08 g, 12.76 mmol) in 150 ml of ethanol and add a slurry of 508 mg of Pd/C (10%) in 20 ml of ethanol. Close the flask with a septum, purge it several times with H<sub>2</sub> and stir it overnight under positive pressure of H<sub>2</sub>. Afterward, filter the slurry through a short pad of celite and evaporate the solution under reduced pressure to give the crude product (4.60 g, 10 98%), which can be used without further purification.

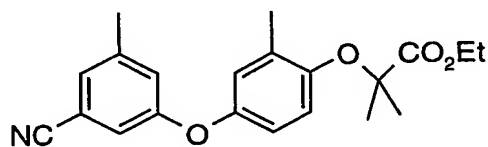
Step D

2-[4-(5-cyano-2-methylphenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester

- Add 30 ml of HCl (2N) to a solution of Step C (2.07 g, 5.63 mmol) in 100 ml of THF-AcOH (9:1) and stir for 5 min. Add 1.7 ml of H<sub>2</sub>O<sub>2</sub> (3%) and then add a 15 solution of sodium nitrite (388 mg, 5.63 mmol) in water (2ml). Stir the mixture at 0°C for 30 min and then at rt for 2 hours. Wash the mixture with saturated solution of sodium bicarbonate for several times until the aqueous layer reaches pH 9. Separate the organic layer and wash it with water and then brine. Dry the organic layer with magnesium sulfate, filter and evaporate the solvent under reduce pressure to give the crude product 20 (1.69 g, 85%). Purify the product by flash chromatography in silica using hexane-ethyl acetate (6:1) as solvent. Mass spectrum (m/e): 354 (M+1)

Intermediate 55

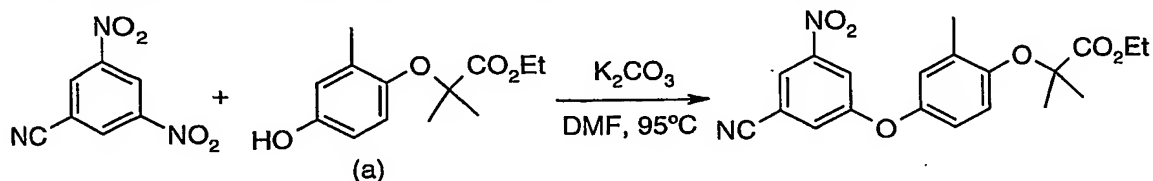
2-[4-(3-cyano-5-methylphenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester





Step A

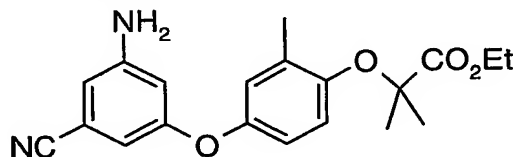
2-[4-(3-cyano-5-nitrophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester



A mixture of 3,5-dinitrobenzonitrile (3.65 g, 18.90 mmol), compound (a) (WO 2003072102) (3 g, 12.60 mmol) and  $K_2CO_3$  (2.1 g, 15.194 mmol) in DMF (40 mL, HPLC grade) is stirred at 95 °C. After 12 h, the mixture is poured into brine, and extracted with EtOAc. The organic layer is dried, filtered and concentrated, and the crude obtained is flash chromatographed on  $SiO_2$  (10 % EtOAc/hexanes) affording 5.54 g of the arylether (94%, white solid).

Step B

2-[4-(3-cyano-5-aminophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester

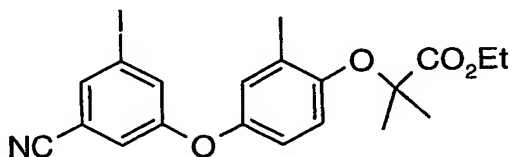


$Pd/C$  (600 mg, 10% Pd on activated C, 0.564 mmol) is added to a solution of the nitro compound from Step B (4.3 g, 11.20 mmol) in EtOH (50 mL, HPLC grade).

The reaction mixture is stirred at r.t. for 2 h under  $H_2$  atmosphere (1 atm). The mixture is filtered through Celite (EtOAc washings), and the solvent is removed in rotatory evaporator. The product purified by flash chromatography on  $SiO_2$  (10-30% EtOAc/hexanes) to afford 3.94 g of the amino compound (99%, colorless oil).

Step C

2-[4-(3-cyano-5-iodophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester



Ter-BuONO (1.5 mL, 12.61 mmol) is added to a 0°C cooled solution of the arylamine from Step B (400 mg, 1.13 mmol) and  $I_2$  (1.72 g, 6.77 mmol) in  $CH_3CN$

(18 mL, HPLC grade). The mixture is allowed to reach r.t., poured into brine, and extracted with TBME. The organic layer is dried, filtered and concentrated. The resulting crude is flash chromatographed on SiO<sub>2</sub> (3% EtOAc/hexanes) to afford 416 mg of the title compound (79%, white solid).

5

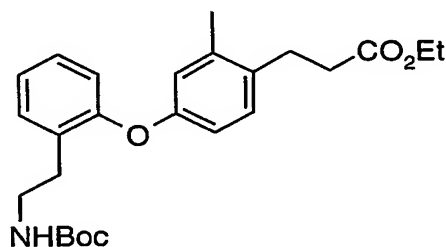
Step D

2-[4-(3-cyano-5-methylphenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester Me<sub>4</sub>Sn (292 mg, 1.631 mmol) is added to a solution of the iodide from Step C (380 mg, 0.8172 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (95 mg, 0.08172 mmol) in DMF (12 mL, anhydrous). The mixture is warmed to 120 °C and stirred at that temperature for 90 min.

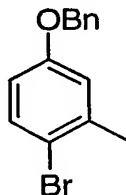
10

It is allowed to reach r.t., filtered through Celite and washed with EtOAc/brine. The organic layer is dried, filtered and concentrated. The crude residue is flash chromatographed on SiO<sub>2</sub> (3-5% EtOAc/hexanes) to afford 270 mg of the title compound (94%, colorless oil).

15

Intermediate 56Step A

3-methyl-4-bromobenzoyloxyphenol

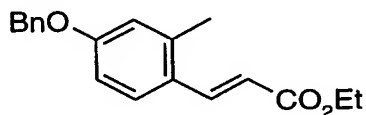


20

Benzyl bromide (3 mL, 25.2 mmol) is added to a suspension of 3-methyl-4-bromophenol (4.7 g, 25.13 mmol) and K<sub>2</sub>CO<sub>3</sub> (3.5 g, 25.32 mmol) in CH<sub>3</sub>CN (40 mL, HPLC grade), and the mixture is stirred at r.t. for 16 h. It is acidified with diluted HCl (1M) and partitioned between EtOAc and H<sub>2</sub>O. The organic layer is dried, filtered and

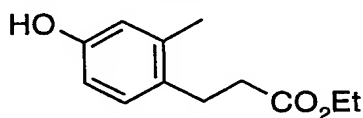
concentrated. The product is purified by flash chromatography on SiO<sub>2</sub> (1-2% EtOAc/hexanes) to afford about 6.5 g of the benzylated phenol (93%, white solid).

Step B



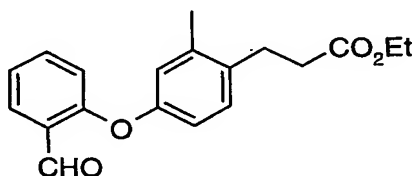
- 5 Ethyl acrylate (12 mL, 114.7 mmol) is added to a solution of 3-methyl-4-bromobenzyloxyphenol (6.5 g, 23.465 mmol), palladium acetate (560 mg, 2.494 mmol), P(o-tol)<sub>3</sub> (1.5 g, 4.928 mmol) and DIPEA (12 mL, 68.89 mmol) in EtCN (120 mL, HPLC grade). The mixture is warmed to 95°C and stirred at that temperature for 60 h. It is allowed to reach r.t., filtered through Celite and partitioned between EtOAc and H<sub>2</sub>O. The organic layer is dried, filtered and concentrated, and the resulting crude is flash chromatographed on SiO<sub>2</sub> (2-3% EtOAc/hexanes) to afford 6.55 g of the Heck product (94%, white solid).

Step C



- 15 Palladium (1.2 g, 10% on activated carbon, 1.127 mmol) is added to a solution of the benzyloxyphenol (6.5 g, 21.96 mmol) in EtOH (120 mL), and the reaction mixture is stirred under H<sub>2</sub> atmosphere (H<sub>2</sub> balloon) overnight (c.a. 14 h). The reaction mixture is filtered through Celite, and the solvent is removed in a rotatory evaporator. The crude residue is flash chromatographed on SiO<sub>2</sub> (5-10-15% EtOAc/hexanes) to afford 4.20 g of the title compound (92%, white solid).

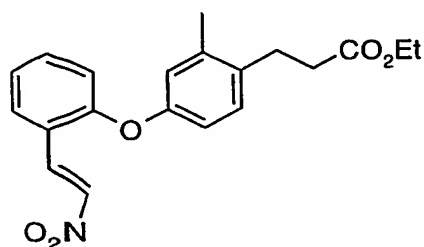
Step D



- 25 A mixture of 2-fluorobenzaldehyde (2.35 g, 18.934 mmol), the compound obtained from Step C (3.5 g, 16.827 mmol) and K<sub>2</sub>CO<sub>3</sub> (1.35 g, 9.76 mmol) in anhydrous DMF (30 mL) is warmed to 140°C, and the mixture is stirred at that temperature for 2 h.

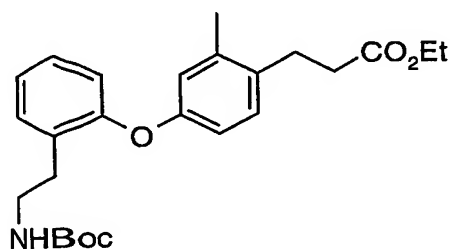
It is allowed to reach r.t. and poured into brine. The organic layer is diluted with EtOAc, washed with brine and water, and then dried, filtered and concentrated. The resulting crude residue is flash chromatographed on SiO<sub>2</sub> (3-5% EtOAc/hexanes) to afford 2.38 g of the substitution product (45%, colorless oil).

5

Step E

Nitromethane (1 mL, 18.46 mmol) is added to a suspension of aldehyde compound obtained from Step D (560 mg, 1.795 mmol) and ammonium acetate (500 mg, 6.486 mmol) in AcOH (glacial, 12 mL), and the mixture is warmed to 115°C. After 5 h, it is allowed to reach r.t., and then neutralized with NaHCO<sub>3</sub> (s) and partitioned between EtOAc and H<sub>2</sub>O. The organic layer is dried, filtered and concentrated to give a crude residue that is flash chromatographed on SiO<sub>2</sub> (3% EtOAc/hexanes) affording 395g of the condensation product (62%, colorless oil).

10

Step F

15

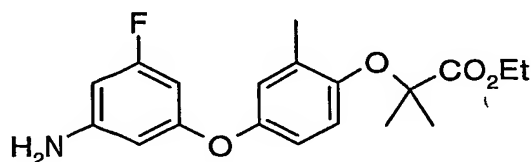
Palladium (100 mg, 10% on activated carbon, 0.094 mmol) is added to a solution of the nitroalkene obtained from Step E (400 mg, 1.1267 mmol) in EtOH (15 mL) and concentrated HCl (1 mL). The mixture is stirred under H<sub>2</sub> atmosphere (H<sub>2</sub> balloon) overnight (c.a. 14 h) and filtered through Celite. The solvent is removed in a rotatory evaporator. The crude residue is dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and Boc<sub>2</sub>O (1 g), and Et<sub>3</sub>N (1.5 mL) are added. The mixture is stirred at r.t. for 2 h, diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with HCl (3% aqueous solution). The organic layer is dried, filtered and

20

concentrated to give a crude that is flash chromatographed on SiO<sub>2</sub> (5% EtOAc/hexanes) to afford 302 mg of the title compound (63%, colorless oil).

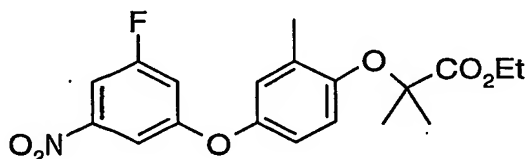
Intermediate 57

5      2-[4-(3-amino-5-fluorophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester



Step A

2-[4-(3-nitro-5-fluorophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester

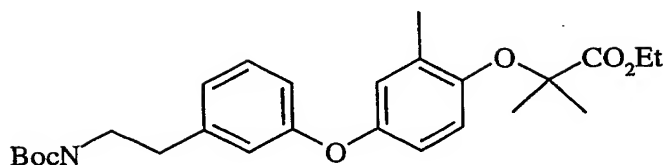
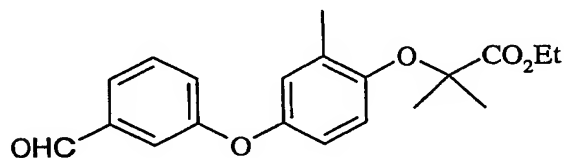


10                      The compound of 3,5-difluoronitrobenzene (1.477 g, 9.28 mmol) is added to a suspension of compound (a) from Intermediate 55, Step A (2 g, 8.4 mmol), KF (4.5 g, 40% in Al<sub>2</sub>O<sub>3</sub>) and 18-crown-6 (210 mg, 0.8 mmol) in CH<sub>3</sub>CN (40 mL). The mixture is warmed to reflux and stirred for 4 h. It is allowed to reach r.t., and partitioned between EtOAc and brine. The organic layer is dried, filtered and concentrated to give a crude  
15      residue that is flash chromatographed on SiO<sub>2</sub> (3-5% EtOAc/hexanes) to afford 2.4 g of the coupling product (76%, colorless oil).

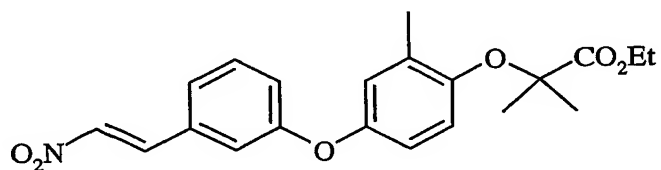
Step B

2-[4-(3-amino-5-fluorophenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester

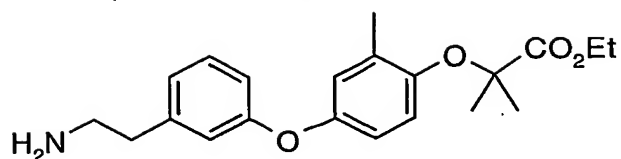
20                      Palladium on carbon (300 mg, 10% Pd on activated C, 0.282 mmol) is added to a solution of nitro compound obtained from Step A (2.4 g, 6.366 mmol) in MeOH (80 mL). The mixture is stirred at r.t. for 2 h under H<sub>2</sub> atmosphere (balloon), and filtered through Celite (EtOAc washings). The solvent is removed in rotary evaporator, and the product is purified by flash chromatography on SiO<sub>2</sub> (10% EtOAc/hexanes) to afford 2.0 g of title compound (90%, colorless oil).

Intermediate 58Step A

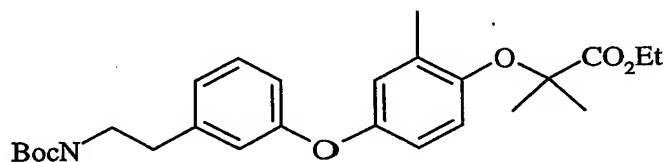
- 5 The compound (a) from Intermediate 55, Step A (1.6 g, 6.722 mmol) and boronic aldehyde (2 g, 13.35 mmol) are added to a suspension of  $\text{Cu}(\text{OAc})_2$  (2.45 g, 13.488 mmol) in a mixture of pyridine (5.4 mL) and  $\text{CH}_2\text{Cl}_2$  (40 mL). The mixture is stirred at r.t. under air atmosphere in the presence of sieves for 36 h. It is filtered through Celite ( $\text{CH}_2\text{Cl}_2$  washings) and partitioned between  $\text{CH}_2\text{Cl}_2$  and diluted HCl (3% aqueous solution). The organic layer is dried, filtered and concentrated to give a crude residue that
- 10 is flash chromatographed on  $\text{SiO}_2$  (5-10% EtOAc/hexanes) affording 0.525 mg of unreacted starting compound (a) and 700 mg of the coupling product (30%, colorless oil).

Step B

- 15 Nitromethane (4 mL, 73.84 mmol) is added to a suspension of aldehyde obtained from Step A (1.3 g, 3.8 mmol) and ammonium acetate (1.2 g, 15.566 mmol) in AcOH (glacial, 15 mL), and the mixture is warmed to 110°C. After 4 h 30 min., it is allowed to reach r.t., neutralized with  $\text{NaHCO}_3$  (s) and partitioned between EtOAc and  $\text{H}_2\text{O}$ . The organic layer is dried, filtered and concentrated to give a crude residue that is
- 20 flash chromatographed on  $\text{SiO}_2$  (10% EtOAc/hexanes) affording 980 mg of the title compound (67%, colorless oil).

Step C

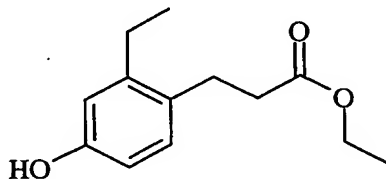
Palladium (100 mg, 10% on activated carbon, 0.094 mmol) is added to a solution of the nitroalkene obtained from Step B (1.0 g, 2.597 mmol) in a mixture of MeOH (25 mL) and concentrated HCl (1 mL). The mixture is stirred under H<sub>2</sub> atmosphere (H<sub>2</sub> balloon) overnight (c.a. 14 h) and filtered through Celite. The solvent is removed in a rotatory evaporator. The crude residue is flash chromatographed on SiO<sub>2</sub> (10-20-30% iPrOH, 0.2% DIPEA/hexanes) to afford 200 mg of the title compound (22%, colorless oil).

Step D

Boc<sub>2</sub>O (165 mg, 0.7575 mmol) and Et<sub>3</sub>N (0.25 mL, 1.82 mmol) are added to a solution of the amine obtained from Step C (180 mg, 0.606 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (12 mL). The mixture is stirred at r.t. for 15 min., diluted with CH<sub>2</sub>Cl<sub>2</sub> and extracted with HCl (3% aqueous solution). The organic layer is dried, filtered and concentrated to give a crude residue that is flash chromatographed on SiO<sub>2</sub> (10-20% EtOAc/hexanes) affording 140 mg of the title compound (58%, colorless oil).

Intermediate 59

3-(2-ethyl-4-hydroxy-phenyl)-propionic acid ethyl ester

Step A: Benzyl protection of 3-ethyl phenol

5           The 3-ethyl phenol (244g, 2.0 mol, 1.0 eq) and benzyl bromide (350.6 g, 2.05 mol, 1.025 eq.) are stirred in a 5-liter flask with 1.0 Liter DMF. A 15°C bath is applied to keep the reaction temperature at 20-25°C. The potassium carbonate (359.6g, 2.6 mol, 1.3 eq) is added with 350 ml DMF, and the mixture is stirred over night (14 hours) at 20-25°C. Tert-butyl methyl ether (MTBE, 650 ml) is added to the mixture. The  
10   solids in the mixture are filtered over a Hyflo pad, and are washed with 650 ml MTBE. The filtrate is washed with a solution 1150 ml 0.35 N HCl. The aqueous layer is back extracted with 500 ml MTBE, and the combined organic layers are washed with 500 ml water and then with 500 ml saturated NaCl solution. The organic layer is dried over magnesium sulfate, and then filtered and evaporated at 40°C on a rotary evaporator to  
15   afford about 424 g light yellow fluid oil.

Step B: N-Bromination

          The starting material (420g, 1.98 mol uncorr., 1 eq) and 1800 ml of acetonitrile are added to a 5L flask and stirred under nitrogen atmosphere. The N-bromosuccinimide (341.8 g, 1.92 mol, 0.97 eq) is added in four to five portions over 15-  
20   20 minutes. A 15°C water bath is applied to the flask to keep the temperature at less than 40°C. The NBS is rinsed into flask with 200 ml ACN. The reaction is stirred for 2 h, over which time the temperature decreased from 37°C to 20°C. The mixture is transferred to a rotary evaporator and evaporated to a mushy oil (app. 900 g). To this oil is added 2000 ml of MTBE, and the mixture is transferred to a separatory funnel. This is  
25   washed once with 750 ml of 1N HCl, once with 750ml of 0.3 N HCl, and once with 500 ml of saturated NaCl solution. The organic layer is dried over MgSO<sub>4</sub>, and then evaporated on a 40°C bath *in vacuo* to afford about 567.8 g of light orange oil.



### Step C: Formylation

The starting material oil (509.2g, 1.75 mol, 1 eq) is dissolved in 1.0 L of THF and dried over night over 4 Å molecular sieves. The solution is filtered into a 12-L 4 neck flask, and rinsed in with 3.0 L THF. Under nitrogen atmosphere, the mixture is cooled to -70 to -72°C. n-Butyl Lithium, 2.5M in hexane (800ml, 2.0 mol, 1.15 eq) are added slowly over 1 hour 40 minutes while keeping the temperature below -68°C. The reaction is then stirred for 5 minutes, and then dry DMF (1L, 12.9 mol, 7.37 eq) is added as quickly as possible, while keeping the temperature below -48°C. The cooling is removed, and the reaction is warmed to -14°C. A solution of 1 N HCl (3.0 L) is added over 3 minutes. The mixture is transferred to a separatory flask and then extracted with 4L diethyl ether, and then with 3.5L diethyl ether. The combined ether layers are washed with a solution of 1L 1N HCl, 1L saturated NaCl solution and 2 L saturated NaCl solution. The ether solution is dried over 500 g magnesium sulfate and then filtered, washed with ether, and evaporated on 40°C bath to a constant weight to afford about 417.4 g brown oil (99.4% weight yield).

### Step D: Horner-Emmons

To a 12 flask fitted with a heating mantle, nitrogen atmosphere, and a stirrer is added 4 L ethanol (2B-3). The potassium carbonate (679.1 g, 4.01 mol, 3.15 equivalents), the aldehyde (375 g, 1.56 mol, 1 equiv.), and triethylphosphonoacetate (454.7 g, 2.03 mol, 1.3 eq) are added to the 12L flask, and then rinsed in with a total of 900 ml ethanol. The reaction is heated to reflux over 30 min., and then refluxed for 2h and 15 min., and then allowed to cool to rt. The mixture is filtered to remove the potassium salts, and the filtrate is evaporated to 1270 g to remove most of the ethanol. The oil is transferred to a separatory flask and added 4L ethyl acetate and washed with 5L 0.6 N HCl. The aqueous layer is back extracted with 4L 0.1N HCl, and then with 2L saturated NaCl solution. The organic layer is dried over magnesium sulfate, filtered, and then evaporated to a dark brown oil on a 40 bath to afford about 565 g.

### Step E: Hydrogenation

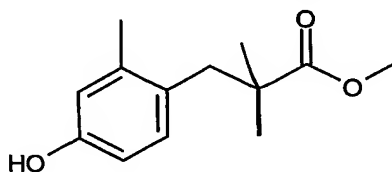
The starting material oil, 1000g (Theo. 2.62 mol from HEW), is dissolved in 4L ethyl acetate and added to a 3-gallon autoclave. About 250 g (42% water wet) of 10% palladium on carbon is added. The mixture is hydrogenated at 50 psi hydrogen

pressure at 50°C. After the reaction is completed, the mixture is cooled to 20-25°C and held under 50 psi hydrogen pressure over night. The catalyst is filtered and washed with 1.5 L ethyl acetate. The solution is evaporated on 40°C bath to yield about 732.2 g of the crude final compound.

5           The final compound is purified as described below. A 5 kg Biotage Flash Chromatography column is pre-conditioned with 10L of 95:5 heptane:ethyl acetate. About 250 g of crude final product (120 wt% yield from Step 4 SM, GC 70%) is loaded on the column with 250 ml 10:1 heptane:ethyl acetate. The column is eluted with 20L of 95:5 heptane:ethyl acetate (4 L fractions) prior to impurities being eluted; then with 20 L  
10 of 95:5 heptane:ethyl acetate (2 L fractions). Fractions are analyzed by TLC (silica; 4:1 heptane:ethyl acetate) and/or by GC. At this point, the fractions contained <95% pure product. The elution is continued with 40 L of 80:20 heptane:ethyl acetate, with 4 L fractions being taken. The fractions containing the final product of <95% purity (by GC) are combined and evaporated to a clear oil (colorless to light yellow). (131.4g, 52.5%  
15 weight recovery, 63.1% yield from Step D, starting material of aldehyde)

#### Intermediate 60

3-(4-Hydroxy-phenyl)-2,2-dimethyl-propionic acid methyl ester



#### Step A

2-Methyl-4-anisaldehyde

20           A mixture of 2,3-dimethylanisole (50g, 0.37 mol), Cu<sup>2+</sup> sulfate pentahydrate (90 g, 0.36 mol), and potassium peroxydisulfate (301 g, 1.11 mol) in acetonitrile/water (1:1, 2.6 L) is stirred vigorously and heated to reflux for 30 minutes.  
25           The reaction is cooled to rt and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4L) and washed with water (2L). The layers are separated, and the aqueous layer is again extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layers are combined and concentrated to afford about 55 g (~100%) product,

which is taken on as is. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 10.05 (s, 1H), 7.78 (m, 1H), 6.95 (m, 1H), 6.88 (s, 1H), 3.84 (s, 3H), 2.6 (s, 3H).

#### Step B

##### 4-Methoxy-2-methylbenzyl alcohol

5                   NaBH<sub>4</sub> (14.82 g, 0.39 mol) is added to a solution of the compound from Step A (55 g, 0.37 mol) in EtOH (800 mL). The reaction is quenched with water (3L), acidified with 5N HCl, and extracted with Et<sub>2</sub>O. The organics are separated and concentrated. The crude product is purified by Biotage 75L (Hexane:EtOAc, 9:1) to afford about 17.35 g (30%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.22 (m, 1H), 6.7 (m, 2H), 4.64 (s, 2H),  
10   3.8 (s, 3H), 2.4 (s, 3H).

#### Step C

##### Acetic acid 4-methoxy-2-methyl-benzyl ester

A solution of compound from Step B (17.35 g, 0.114 mol) in CH<sub>2</sub>Cl<sub>2</sub> (900 mL) is cooled 0°C, and TEA (23.3 mL, 0.167 mol) and acetyl chloride (9.3 mL, 0.131  
15   mol) are added. The reaction is stirred for 1 h and then quenched with 1N HCl, washed with aq. NaHCO<sub>3</sub>, brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to afford an oil (22.14 g, ~100%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.24 (m, 1H), 6.73 (m, 2H), 5.08 (s, 2H), 3.8 (s, 3H), 2.33 (s, 3H), 2.08 (s, 3H).

#### Step D

20               3-(4-Methoxy-2-methyl-phenyl)-2,2-dimethyl-propionic acid methyl ester

The compound from Step C (22.14 g, 0.114 mol) is dissolved in CH<sub>2</sub>Cl<sub>2</sub> and treated with 1-methoxy-1-trimethylsiloxy-2-methyl-1-propene (53.3 g, 0.306 mol) and Mg(ClO<sub>4</sub>)<sub>2</sub> (2.58 g, 0.012 mol). The reaction is stirred overnight at rt. Upon completion, the reaction is washed with water, brine, and dried with Na<sub>2</sub>SO<sub>4</sub>. The crude  
25   product is purified (Biotage 75M (Hexane:EtOAc, 9:1@ 8:2)) to obtain about 18.7 g (70%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 6.97 (d, 1H), 6.7 (m, 2H), 3.8 (s, 3H), 3.64 (s, 3H), 2.85 (s, 2H), 2.3 (s, 3H), 1.2 (s, 6H).

#### Step E

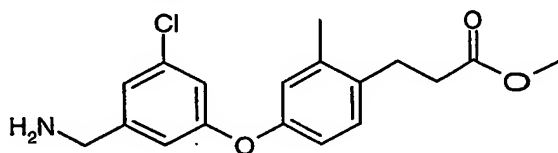
##### 3-(4-Hydroxy-phenyl)-2,2-dimethyl-propionic acid methyl ester

30               BBr<sub>3</sub> (1M in CH<sub>2</sub>Cl<sub>2</sub>, 79 ml) is cooled to 0°C, and the compound from Step D (9.35 g, 0.0395 mol) is added dropwise over 10 minutes. After stirring for 1 h at

0°C, the reaction is quenched with 1:1 MeOH: CH<sub>2</sub>Cl<sub>2</sub>. The organics are concentrated, and the resulting oil is run through a plug of silica gel with Hexane:EtOAc (8:2). Fractions 1,2 are concentrated and about 7.5 g (85%) of the desired compound are isolated. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 6.87 (d, 1H), 6.6 (m, 2H), 4.9 (bs, 1H), 3.64 (s, 3H), 2.82 (s, 2H), 2.22 (s, 3H), 1.2 (s, 6H).

#### Intermediate 61

3-[4-(3-Aminomethyl-5-chloro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester



The title compound is prepared according to the procedure described in Intermediate 33 utilizing 3-chloro-5-fluorobenzonitrile and 3-(4-hydroxy-2-methylphenyl)-propionic acid methyl ester (*J.Chem.Soc.Perkin Trans. 1*; 4; 1990; 1041-1045). MS: (ES<sup>+</sup>) 334 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

#### Example 1

##### General Procedures for Coupling and Hydrolysis

##### Step A-Coupling Step

Acid (1.0 eq), amine (1.0-1.5 eq), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.2-1.5 eq), 1-hydroxybenzotriazole hydrate (1.2-1.5 eq), and *N,N*-diisopropylethylamine (1.0 eq) are stirred overnight under nitrogen at rt in dry THF or dry DMF. Water is added, extracted with ethyl acetate, washed with 1 N HCl, then saturated sodium bicarbonate, followed by brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography, eluting with 10-15 % EtOAc in hexane then 25 % EtOAc in hexane provides the intermediate ester shown in the above general procedure.

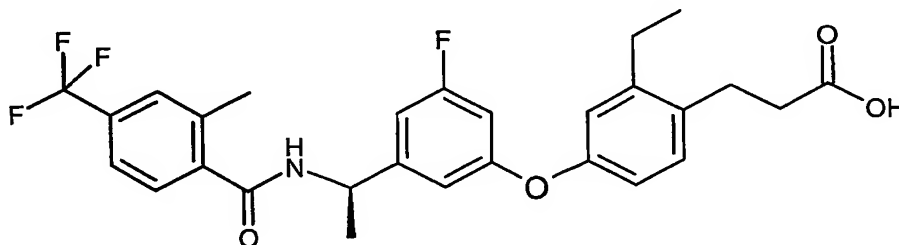
##### Step B-Hydrolysis Step

Compound from Step A (1 eq) is hydrolyzed in dioxane/water (2:1 v/v, ~0.02M) with lithium hydroxide hydrate (7-13 eq). Reaction is stirred at rt overnight under nitrogen, and then acidified with 5 N HCl. Water is added, extracted with EtOAc,

washed with brine, dried over sodium sulfate and concentrated under reduced pressure to give the final acid.

### Example 2

5 3-(2-Ethyl-4-{3-fluoro-5-[1-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenyl)-propionic acid



### Step A

10 3-(2-Ethyl-4-{3-fluoro-5-[1-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenyl)-propionic acid ethyl ester  
 2-Methyl-4-trifluoromethyl-benzoic acid (41.3 mg, 0.20 mmol), 3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester (Intermediate 23) (80.0 mg, 0.23 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (46.5 mg, 0.24 mmol), 1-hydroxybenzotriazole hydrate (32.8 mg, 0.24 mmol), and *N,N*-diisopropylethylamine (0.035 mL, 0.20 mmol) are stirred overnight under nitrogen at rt in dry THF (8 mL). Water is added, extracted with ethyl acetate, washed with 1 N HCl, then saturated sodium bicarbonate, followed by brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography, eluting with 15 % EtOAc in hexane then 25 % EtOAc in hexane provides the title compound (84.1 mg, 76 %). MS(ES<sup>+</sup>): 546 (M+H<sup>+</sup>); <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>)

### Step B

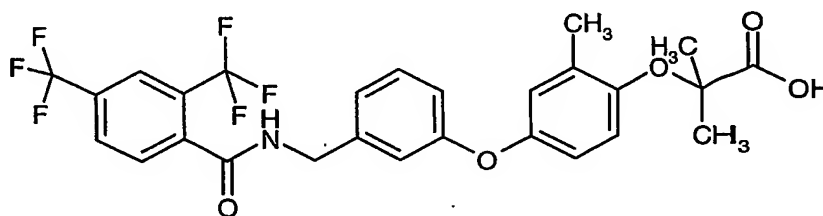
25 3-(2-Ethyl-4-{3-fluoro-5-[1-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenyl)-propionic acid  
 Compound of Step A (84.1 mg, 0.15 mmol) is dissolved in dioxane (6 mL) and lithium hydroxide hydrate (85 mg, 2.02 mmol), dissolved in water (3 mL), is added. Reaction is stirred at rt overnight under nitrogen, then acidified with 5 N HCl. Water is

added, extracted with EtOAc, washed with brine, dried over sodium sulfate and concentrated under reduced pressure to give the title compound (66.4 mg, 84 %). Exact mass calculated for  $C_{28}H_{28}F_4NO_4$  ( $M+H^+$ ) 518.1954, found 518.1956;  $^1NMR$  (400 MHz,  $CDCl_3$ ).

5

### Example 3

2-(4-{3-[(2,4-Bis-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



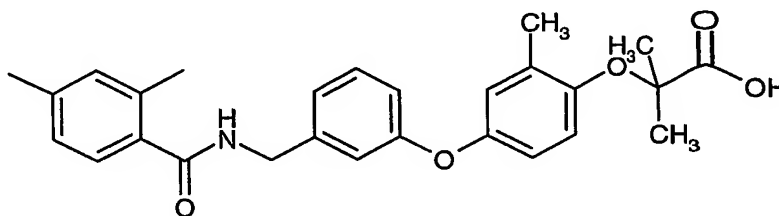
10

The title compound is prepared according to Example 1 utilizing 2,4-bis-trifluoromethyl-benzoic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{27}H_{24}F_6NO_5$  ( $M+H^+$ ): 556.1559, found 556.1561;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

15

### Example 4

2-(4-{3-[(2,4-Dimethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid

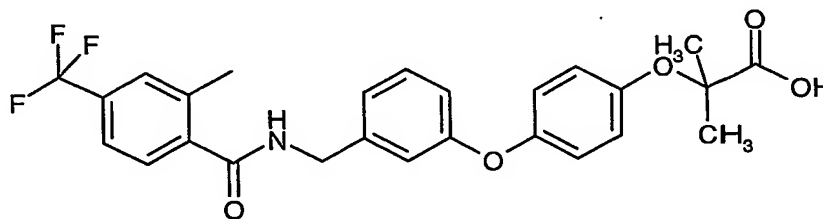


20

The title compound is prepared according to Example 1 utilizing 2,4-dimethyl-benzoic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{27}H_{30}NO_5$  ( $M+H^+$ ): 448.2240, found 448.2118;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 5

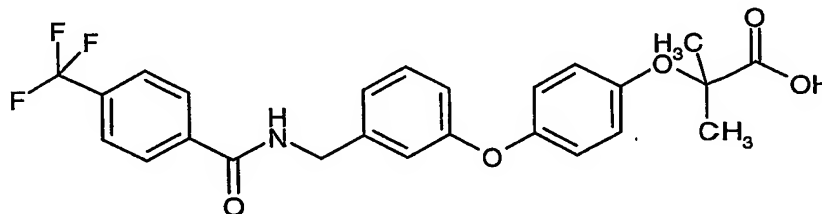
2-Methyl-2-(4-{3-[(2-methyl-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid



5 The title compound is prepared according to Example 1 utilizing 2-methyl-4-trifluoromethyl-benzoic acid (Intermediate 10) and 2-[4-(3-aminomethyl-phenoxy)-phenoxy]-2-methyl-propionic acid (Intermediate 49). Exact mass calcd for  $C_{26}H_{25}F_3NO_5$  ( $M+H^+$ ): 488.1685, found 488.1674;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 6

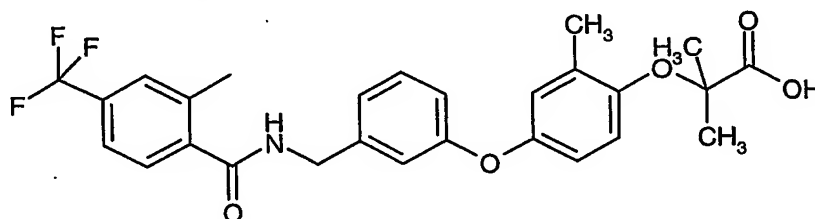
10 2-Methyl-2-(4-{3-[(4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid



15 The title compound is prepared according to Example 1 utilizing 4-trifluoromethyl-benzoic acid and 2-[4-(3-aminomethyl-phenoxy)-phenoxy]-2-methyl-propionic acid (Intermediate 49). Exact mass calcd for  $C_{25}H_{23}F_3NO_5$  ( $M+H^+$ ): 474.1588, found 474.1505;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 7

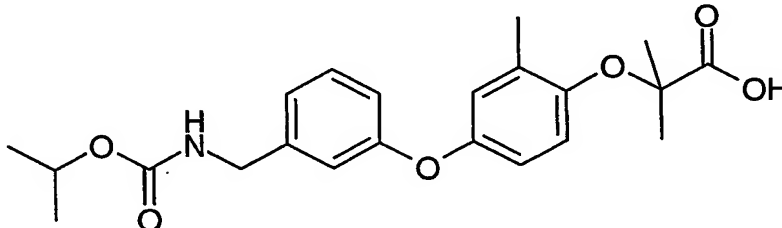
2-Methyl-2-(2-methyl-4-{3-[(2-methyl-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid



5 The title compound is prepared according to Example 1 utilizing 2-methyl-4-trifluoromethyl-benzoic acid (Intermediate 10) and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{27}H_{27}F_3NO_5$  ( $M+H^+$ ): 502.1841, found 502.1844;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 8

10 2-{4-[3-(Isopropoxycarbonylamino-methyl)-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid

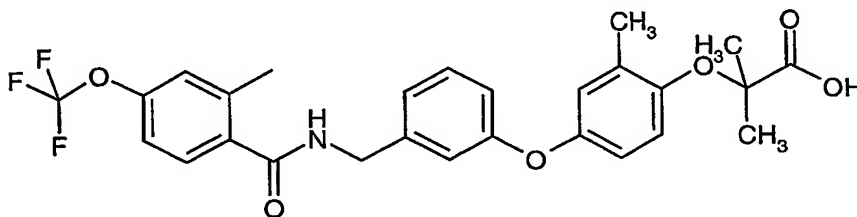


15 The title compound is prepared according to the general procedures described in Example 140 utilizing isopropyl chloroformate and 2-[4-(3-aminomethylphenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester (Intermediate 17). Mass ( $ES^+$ ): 402.3 ( $M+H^+$ ).



Example 9

2-Methyl-2-(2-methyl-4-{3-[(2-methyl-4-trifluoromethoxy-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid

Step A

2-Methyl-2-(2-methyl-4-{3-[(2-methyl-4-trifluoromethoxy-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid ethyl ester

The compound of 2-methyl-4-trifluoromethoxy-benzoic acid (30.0 mg, 0.14 mmol) (Intermediate 13), 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17) (47.0 mg, 0.14 mmol), *o*-(7-azobenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (62.0 mg, 0.16 mmol), and *N,N*-diisopropylethylamine (0.023 mL, 0.14 mmol) are stirred overnight under nitrogen at rt in DCM (3 mL) and dry DMF (0.5 mL). Water is added, and the mixture is extracted with ethyl acetate. The mixture is washed with 1 N HCl and saturated sodium bicarbonate and brine, and then dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography, eluting with 15 % EtOAc in hexane and then 25 % EtOAc in hexane provides the title compound (41 mg, 55 %). MS(ES<sup>+</sup>): 546 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

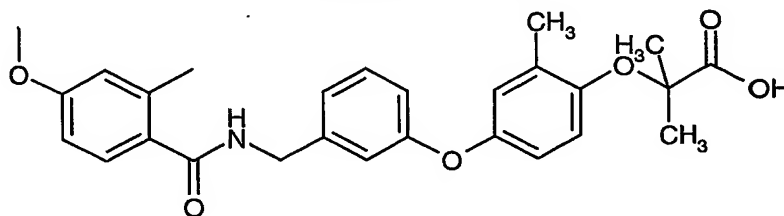
Step B

2-Methyl-2-(2-methyl-4-{3-[(2-methyl-4-trifluoromethoxy-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid

Compound of Step A (41.0 mg, 0.075 mmol) is dissolved in dioxane (4 mL) and lithium hydroxide hydrate (62.0 mg, 1.5 mmol), dissolved in water (2 mL), is added. Reaction is stirred at rt overnight under nitrogen, and then acidified with 5 N HCl. Water is added and the mixture is extracted with EtOAc, which is washed with brine, dried over sodium sulfate and concentrated under reduced pressure to give the title compound (35.0 mg, 90 %). Exact mass calcd for C<sub>27</sub>H<sub>27</sub>F<sub>3</sub>NO<sub>6</sub> (M+H<sup>+</sup>): 518.1790, found 518.1797; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Example 10

2-(4-{3-[(4-Methoxy-2-methyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid

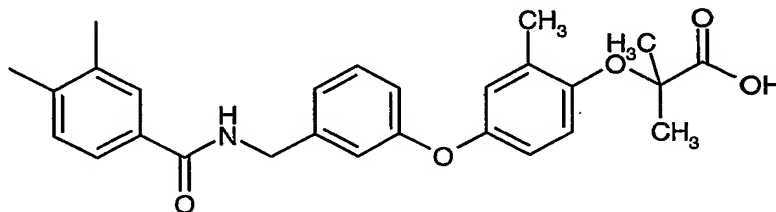


5 The title compound is prepared according to Example 1 utilizing 2-methyl-4-methoxy-benzoic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{27}H_{30}NO_6$  ( $M+H^+$ ): 464.2073, found 464.2082;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 11

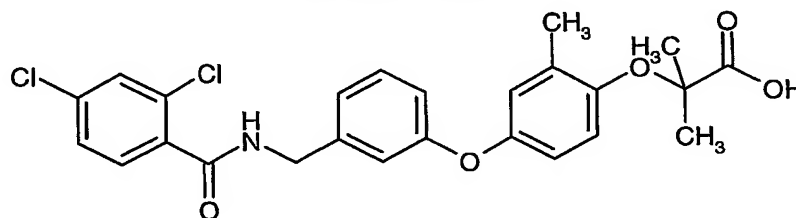
2-(4-{3-[(3,4-Dimethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



15 The title compound is prepared according to Example 1 utilizing 3,4-dimethyl-benzoic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{27}H_{30}NO_5$  ( $M+H^+$ ): 448.2124, found 448.2126;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 12

2-(4-{3-[(2,4-Dichloro-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid

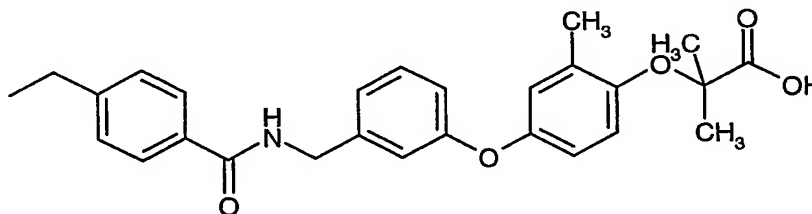


5           The title compound is prepared according to Example 1 utilizing 2,4-dichloro-benzoic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{25}H_{24}Cl_2NO_5$  ( $M+H^+$ ): 488.1032, found 488.1041;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 13

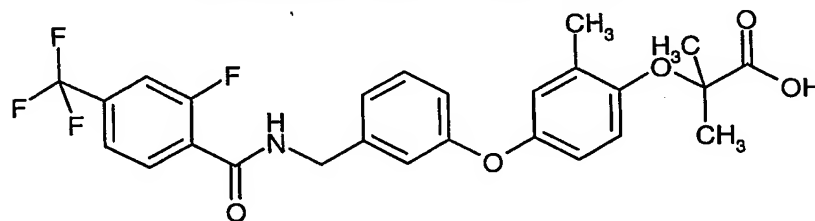
2-(4-{3-[(4-Ethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



15           The title compound is prepared according to Example 1 utilizing 4-ethylbenzoic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{27}H_{30}NO_5$  ( $M+H^+$ ): 448.2124, found 448.2099;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 14

2-(4-{3-[(2-Fluoro-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



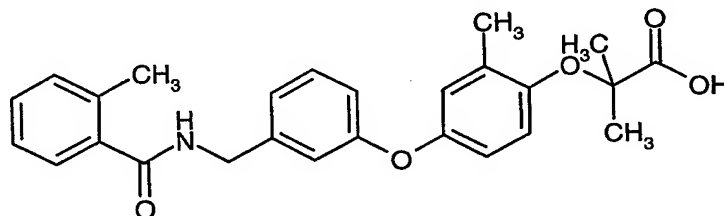
5

The title compound is prepared according to Example 1 utilizing 2-fluoro-4-trifluoromethyl-benzoic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{26}H_{24}F_4NO_5$  ( $M+H^+$ ): 506.1591, found 506.1581;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 15

2-Methyl-2-(2-methyl-4-{3-[(2-methyl-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid

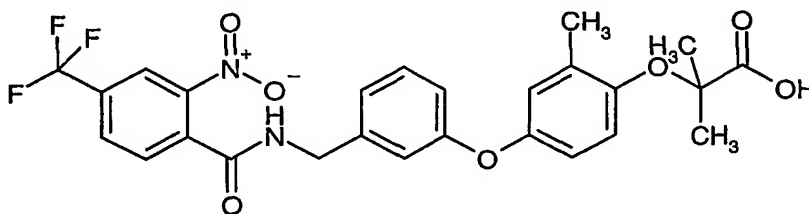


15

The title compound is prepared according to Example 1 utilizing 2-methylbenzoic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{26}H_{28}NO_5$  ( $M+H^+$ ): 434.1967, found 434.1954;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 16

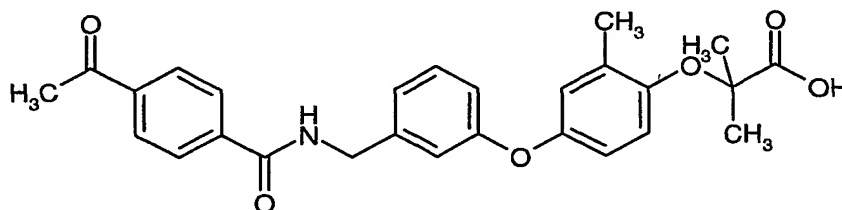
2-Methyl-2-(2-methyl-4-{3-[(2-nitro-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid



The title compound is prepared according to Example 1 utilizing 2-nitro-4-trifluoromethyl-benzoic acid (US Pat. No. 4,868,833) and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{26}H_{24}F_3N_2O_7$  ( $M+H^+$ ): 533.1536, found 533.1518;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 17

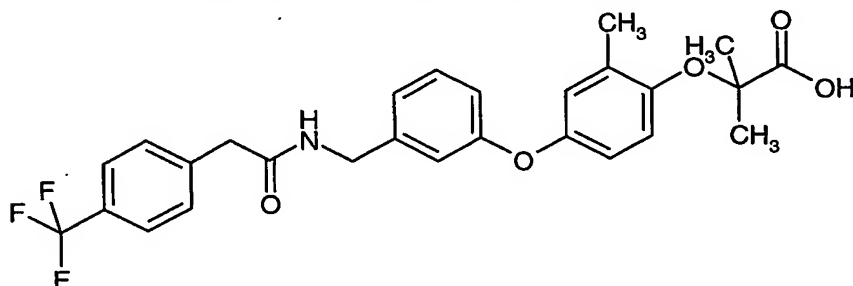
2-(4-{3-[(4-Acetyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



The title compound is prepared according to Example 1 utilizing 4-acetylbenzoic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{27}H_{28}NO_6$  ( $M+H^+$ ): 462.1897, found 462.1917;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 18

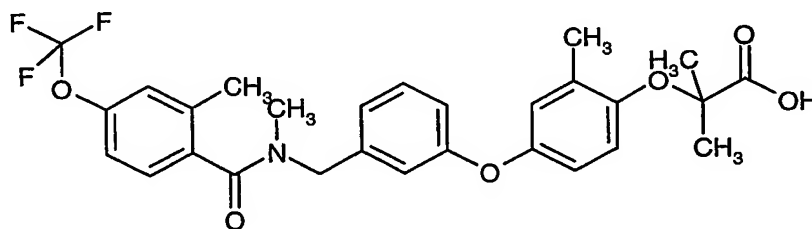
2-Methyl-2-[2-methyl-4-(3-[[2-(4-trifluoromethyl-phenyl)-acetyl-amino]-methyl]-phenoxy)-phenoxy]-propionic acid



The title compound is prepared according to Example 1 utilizing (4-trifluoromethyl-phenyl)-acetic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{27}H_{27}F_3NO_5$  ( $M+H^+$ ): 502.1841, found 502.1832;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 19

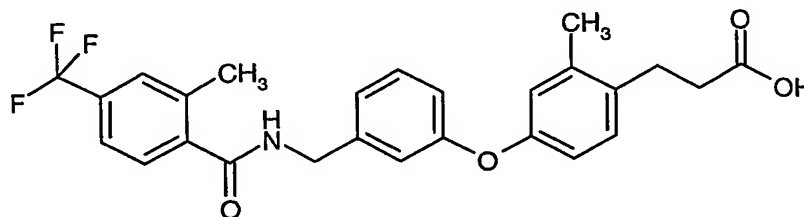
2-Methyl-2-[2-methyl-4-(3-[[methyl-(2-methyl-4-trifluoromethoxy-benzoyl)-amino]-methyl]-phenoxy)-phenoxy]-propionic acid



The ethyl ester of the title compound is prepared according to Intermediate 2, Step A by utilizing 2-ethyl-2-(2-methyl-4-{3-[(2-methyl-4-trifluoromethoxy-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid ethyl ester (Example 9, Step A), and is then hydrolyzed according to Example 9, Step B, providing the title compound. Exact mass calcd for  $C_{28}H_{29}F_3NO_6$  ( $M+H^+$ ): 532.1947, found 532.1921;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 20

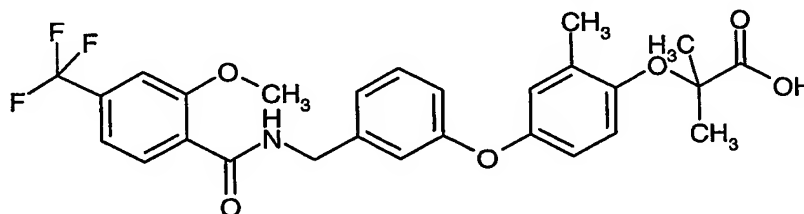
3-(2-Methyl-4-{3-[(2-methyl-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenyl)-propionic acid



5 The title compound is prepared according to Example 1 utilizing 2-methyl-4-trifluoromethyl-benzoic acid (Intermediate 10) and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{26}H_{25}F_3NO_4$  ( $M+H^+$ ): 472.1736, found 472.1744;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 21

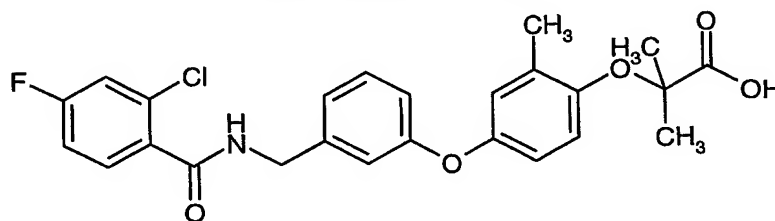
10 2-(4-{3-[(2-Methoxy-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



15 The title compound is prepared according to Example 1 utilizing 2-methoxy-4-trifluoromethyl-benzoic acid (*J.Am.Chem.Soc.*; 73; 1951; 2375) and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{27}H_{27}F_3NO_6$  ( $M+H^+$ ): 518.1790, found 518.1788;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 22

2-(4-{3-[(2-Chloro-4-fluorobenzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid

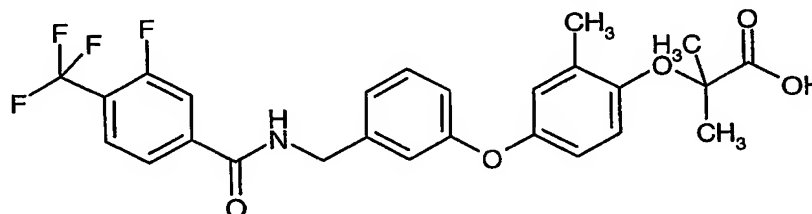


5 The title compound is prepared according to Example 1 utilizing 2-chloro-4-fluorobenzoic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{25}H_{24}ClFNO_5$  ( $M+H^+$ ): 472.1327, found 472.1322;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 23

2-(4-{3-[(3-Fluoro-4-trifluoromethylbenzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid

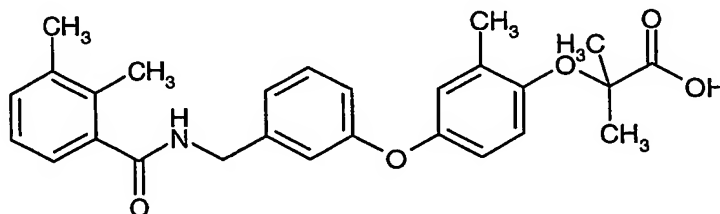


15 The title compound is prepared according to Example 1 utilizing 3-fluoro-4-trifluoromethylbenzoic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{26}H_{24}F_4NO_5$  ( $M+H^+$ ): 506.1591, found 506.1593;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).



Example 24

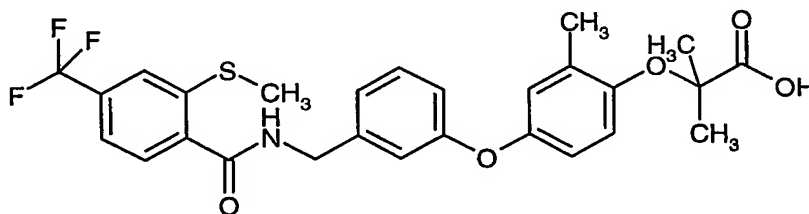
2-(4-{3-[(2,3-Dimethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



The title compound is prepared according to Example 1 utilizing 2,3-dimethyl-benzoic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{27}H_{30}NO_5$  ( $M+H^+$ ): 448.2124, found 448.2111;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 25

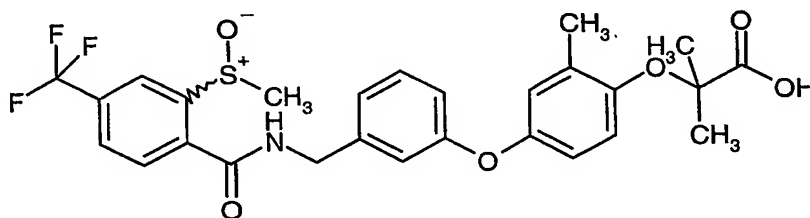
2-Methyl-2-(2-methyl-4-{3-[(2-methylsulfanyl-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid



The title compound is prepared according to Example 1 utilizing 2-methylsulfanyl-4-trifluoromethyl-benzoic acid (WO 9902489) and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{27}H_{27}F_3NO_5S$  ( $M+H^+$ ): 534.1562, found 534.1542;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 26

2-(4-{3-[(2-Methanesulfinyl-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid

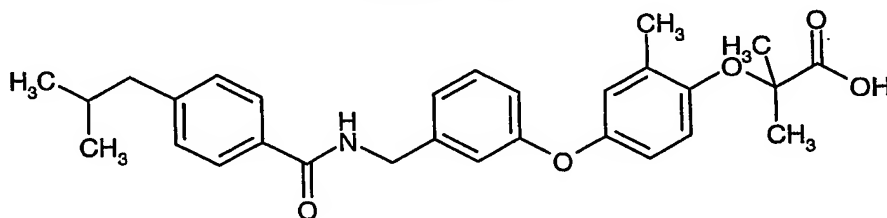


- 5 The compound of 2-methyl-2-(2-methyl-4-{3-[(2-methylsulfonyl-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid (61.7 mg, 0.12mmol) (Example 25) is dissolved in chloroform (5 mL), cooled in an ice bath, and solid 3-chloroperoxybenzoic acid (77 %) (24.7 mg, 0.11mmol) is added. Solution is stirred for 15 minutes and quenched with water and then extracted with dichloromethane.
- 10 The solution is washed with sodium bicarbonate, brine, and then dried with sodium sulfate and concentrated under reduced pressure providing the title compound (18.6 mg, 30 %) without further purification. Exact mass calcd for  $C_{27}H_{27}F_3NO_6S$  ( $M+H^+$ ): 550.1511, found 550.1490;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

15

Example 27

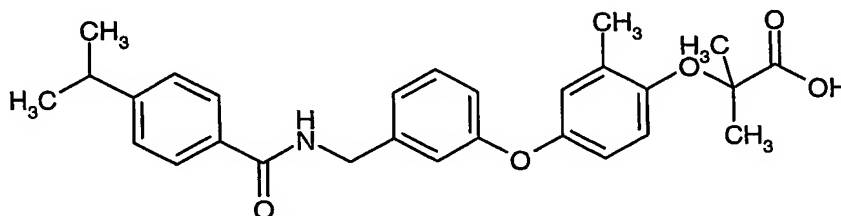
2-(4-{3-[(4-Isobutyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



- The title compound is prepared according to Example 1 utilizing 4-isobutyl-benzoic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{29}H_{34}NO_5$  ( $M+H^+$ ): 476.2437, found 476.2437;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).
- 20

### Example 28

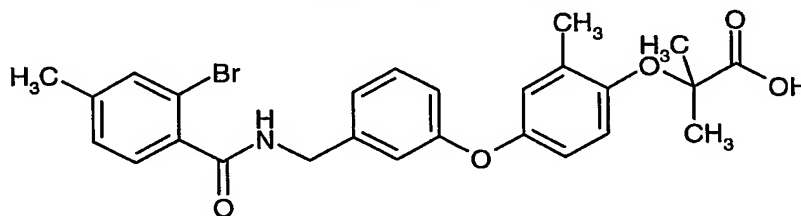
2-(4-{3-[(4-Isopropyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



The title compound is prepared according to Example 1 utilizing 4-isopropyl-benzoic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{28}H_{32}NO_5$  ( $M+H^+$ ): 462.2299, found 462.2280;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

### Example 29

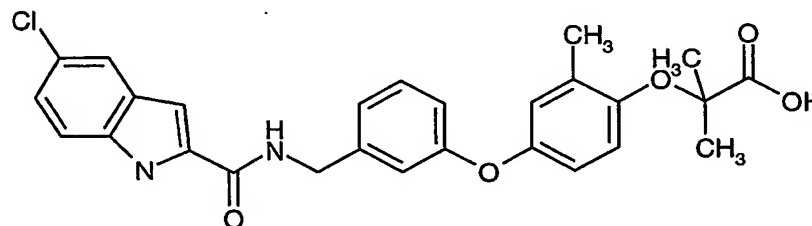
2-(4-{3-[(2-Bromo-4-methyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



The title compound is prepared according to Example 1 utilizing 2-bromo-4-methyl-benzoic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for C<sub>26</sub>H<sub>27</sub>BrNO<sub>5</sub> (M+H<sup>+</sup>): 512.1073, found 512.1069; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Example 30

2-[4-(3-[(5-Chloro-1H-indole-2-carbonyl)-amino]-methyl)-phenoxy]-2-methyl-  
phenoxy]-2-methyl-propionic acid

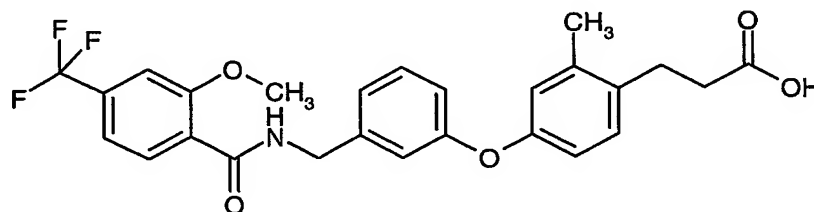


5 The title compound is prepared according to Example 1 utilizing 5-chloro-1H-indole-2-carboxylic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{27}H_{26}ClN_2O_5$  ( $M+H^+$ ): 493.1530, found 493.1547;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 31

3-(4-{3-[(2-Methoxy-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-  
phenyl)-propionic acid

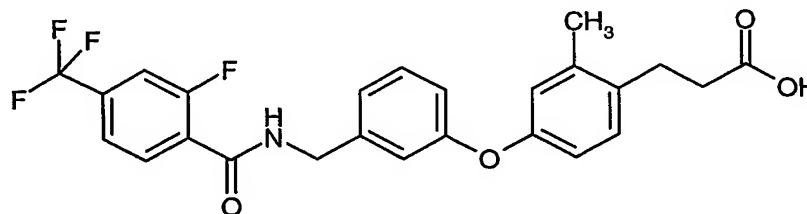


15 The title compound is prepared according to Example 1 utilizing 2-methoxy-4-trifluoromethyl-benzoic acid (*J.Am.Chem.Soc.*; 73; 1951; 2375) and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{26}H_{25}F_3NO_5$  ( $M+H^+$ ): 488.1685, found 488.1680;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

20

Example 32

3-(4-{3-[(2-Fluoro-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenyl)-propionic acid

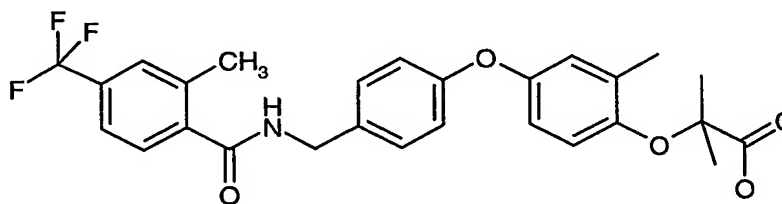


5 The title compound is prepared according to Example 1 utilizing 2-fluoro-4-trifluoromethyl-benzoic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{25}H_{22}F_4NO_4$  ( $M+H^+$ ): 476.1485, found 476.1503;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 33

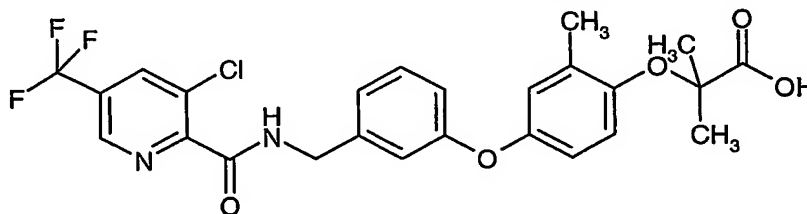
2-Methyl-2-(2-methyl-4-{4-[(2-methyl-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid



15 The title compound is prepared according to Example 1 utilizing 2-methyl-4-trifluoromethyl-benzoic acid (Intermediate 10) and 2-[4-(4-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 18). Exact mass calcd for  $C_{27}H_{27}F_3NO_5$  ( $M+H^+$ ): 502.1841, found 502.1832;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 34

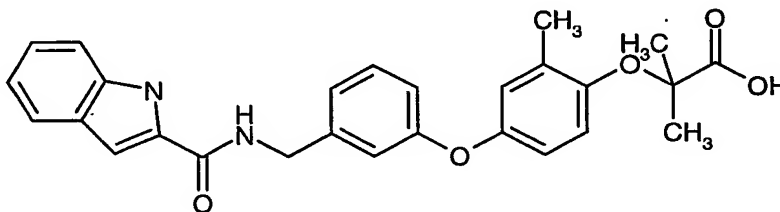
2-[4-(3-[[3-Chloro-5-trifluoromethyl-pyridine-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenoxy]-2-methyl-propionic acid



The title compound is prepared according to Example 1 utilizing 3-chloro-5-trifluoromethyl-pyridine-2-carboxylic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{25}H_{23}ClF_3N_2O_5$  ( $M+H^+$ ): 523.1248, found 523.1247;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 35

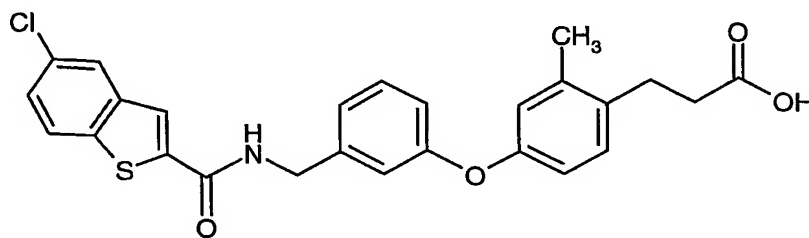
2-[4-(3-[[1H-Indole-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenoxy]-2-methyl-propionic acid



The title compound is prepared according to Example 1 utilizing 1H-indole-2-carboxylic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{27}H_{27}N_2O_5$  ( $M+H^+$ ): 459.1290, found 459.1918;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 36

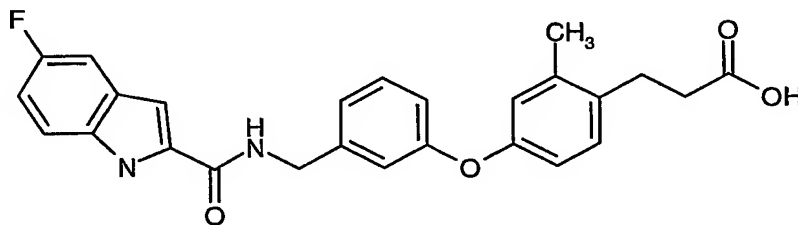
3-[4-(3-[[5-Chloro-benzo[b]thiophene-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid



5 The title compound is prepared according to Example 1 utilizing 5-chloro-benzo[b]thiophene-2-carboxylic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{26}H_{23}ClNO_4S$  ( $M+H^+$ ): 480.1036, found 480.1016;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 37

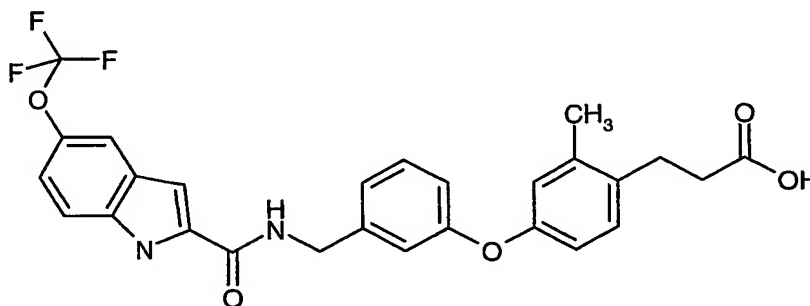
10 3-[4-(3-[[5-Fluoro-1H-indole-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid



15 The title compound is prepared according to Example 1 utilizing 5-fluoro-1H-indole-2-carboxylic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{26}H_{24}FN_2O_4$  ( $M+H^+$ ): 447.1720, found 447.1720;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 38

3-[2-Methyl-4-(3-{[(5-trifluoromethoxy-1H-indole-2-carbonyl)-amino]-methyl}-phenoxy)-phenyl]-propionic acid

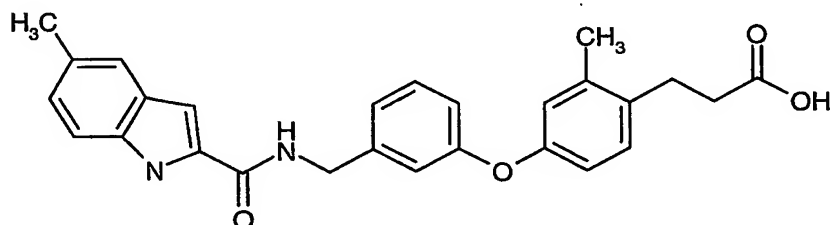


5 The title compound is prepared according to Example 1 utilizing 5-trifluoromethoxy-1H-indole-2-carboxylic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{27}H_{24}F_3N_2O_5$  ( $M+H^+$ ): 513.1637, found 513.1647;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 39

3-[2-Methyl-4-(3-{[(5-methyl-1H-indole-2-carbonyl)-amino]-methyl}-phenoxy)-phenyl]-propionic acid

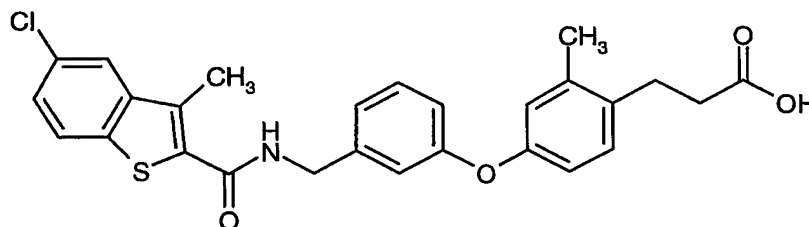


15 The title compound is prepared according to Example 1 utilizing 5-methyl-1H-indole-2-carboxylic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{27}H_{27}N_2O_4$  ( $M+H^+$ ): 443.1971, found 443.1966;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).



Example 40

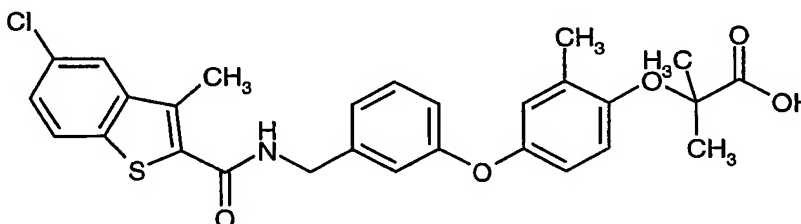
3-[4-(3-[[[(5-Chloro-3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-methyl]-phenoxy]-2-methyl-phenyl]-propionic acid



The title compound is prepared according to Example 1 utilizing 5-chloro-3-methyl-benzo[b]thiophene-2-carboxylic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{27}H_{25}ClNO_4S$  ( $M+H^+$ ): 494.1193, found 494.1189;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 41

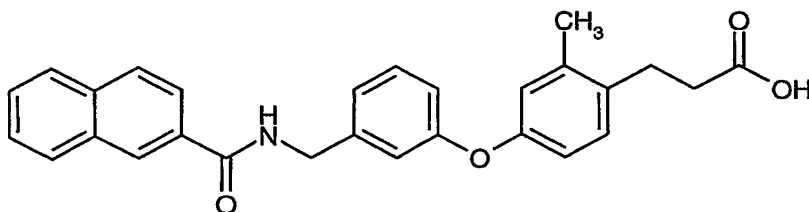
2-[4-(3-[[[(5-Chloro-3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-methyl]-phenoxy]-2-methyl-phenoxy]-2-methyl-propionic acid



The title compound is prepared according to Example 9 utilizing 5-chloro-3-methyl-benzo[b]thiophene-2-carboxylic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{28}H_{27}ClNO_5S$  ( $M+H^+$ ): 524.1298, found 524.1304;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 42

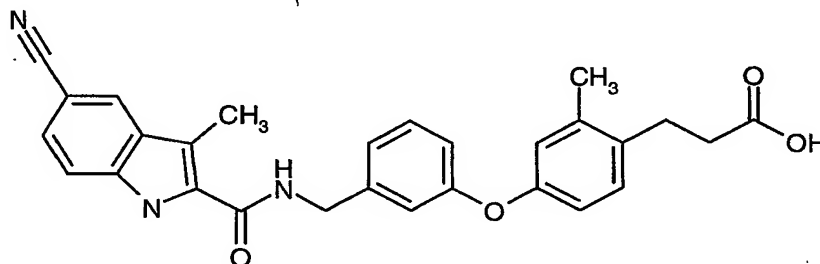
3 3-[2-Methyl-4-(3-[[naphthalene-2-carbonyl]-amino]-methyl)-phenoxy]-phenyl]-  
propionic acid



5 The title compound is prepared according to Example 1 utilizing naphthalene-2-carboxylic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{28}H_{26}NO_4$  ( $M+H^+$ ): 440.1862, found 440.1873;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 43

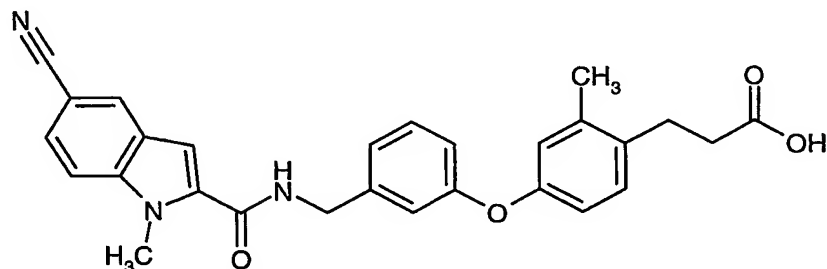
10 3-[4-(3-[[5-Cyano-3-methyl-1H-indole-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid



15 The title compound is prepared according to Example 1 utilizing 5-cyano-3-methyl-1H-indole-2-carboxylic acid (*J. Med. Chem.* 1997, 40 (18), 2843-2857) and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{28}H_{26}N_3O_4$  ( $M+H^+$ ): 468.1923, found 468.1903;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 44

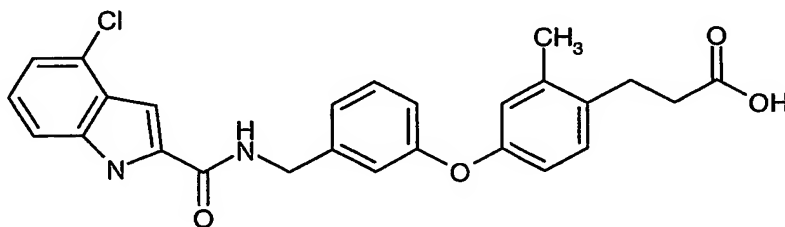
3-[4-(3-[[5-Cyano-1-methyl-1H-indole-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid



The title compound is prepared according to Example 1 utilizing 5-cyano-1-methyl-1H-indole-2-carboxylic acid (*J. Med. Chem.* 1997, 40 (18), 2843-2857) and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{28}H_{26}N_3O_4$  ( $M+H^+$ ): 468.1923, found 468.1903;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 45

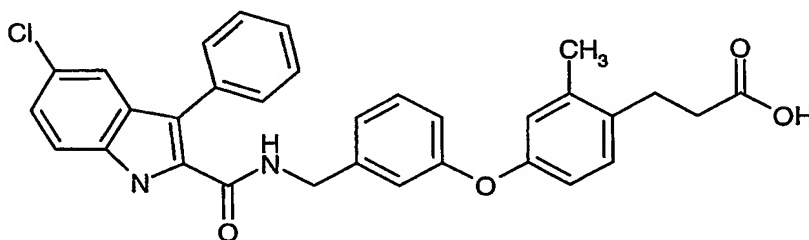
3-[4-(3-[[4-Chloro-1H-indole-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid



The title compound is prepared according to Example 1 utilizing 4-chloro-1H-indole-2-carboxylic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{26}H_{24}ClN_2O_4$  ( $M+H^+$ ): 463.1425, found 463.1399;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 46

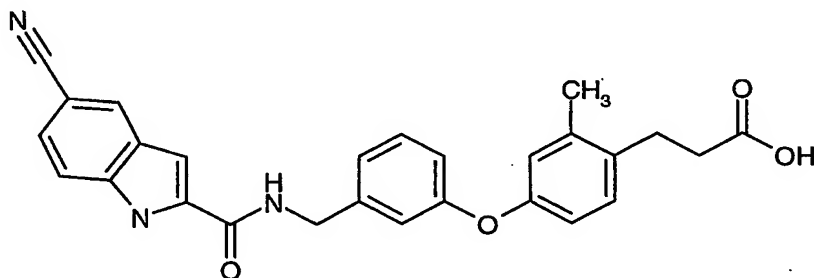
3-[4-(3-[[[(5-Chloro-3-phenyl-1H-indole-2-carbonyl)-amino]-methyl]-phenoxy]-2-methyl-phenyl]-propionic acid



5 The title compound is prepared according to Example 1 utilizing 5-chloro-3-phenyl-1H-indole-2-carboxylic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{32}H_{28}ClN_2O_4$  ( $M+H^+$ ): 539.1738, found 539.1736;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 47

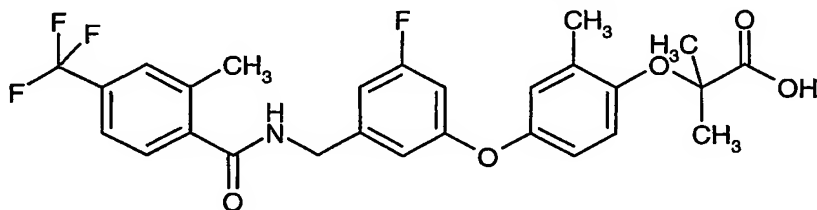
10 3-[4-(3-[[[(5-Cyano-1H-indole-2-carbonyl)-amino]-methyl]-phenoxy]-2-methyl-phenyl]-propionic acid



15 The title compound is prepared according to Example 9 utilizing 5-cyano-1H-indole-2-carboxylic acid (*J. Med. Chem.* 1997, 40 (18), 2843-2857) and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{27}H_{24}N_3O_4$  ( $M+H^+$ ): 454.1767, found 454.1743;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 48

2-(4-{3-Fluoro-5-[(2-methyl-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid

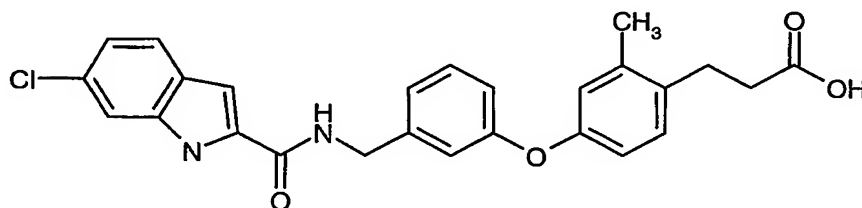


5           The title compound is prepared according to Example 1 utilizing 2-methyl-4-trifluoromethyl-benzoic acid (Intermediate 10) and 2-[4-(3-aminomethyl-5-fluorophenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 47). Exact mass calcd for  $C_{27}H_{26}F_4NO_5$  ( $M+H^+$ ): 520.1747, found 520.1747;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 49

3-[4-(3-{[(6-Chloro-1H-indole-2-carbonyl)-amino]-methyl}-phenoxy)-2-methyl-phenyl]-propionic acid

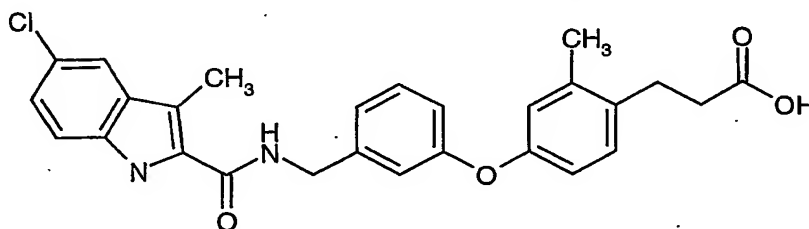


15           The title compound is prepared according to Example 1 utilizing 6-chloro-1H-indole-2-carboxylic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{26}H_{24}ClN_2O_4$  ( $M+H^+$ ): 463.1425, found 463.1427;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

20

Example 50

3-[4-(3-[[5-Chloro-3-methyl-1H-indole-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid

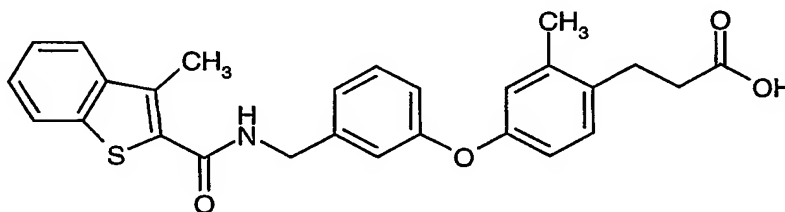


5 The title compound is prepared according to Example 1 utilizing 5-chloro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 3) and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{27}H_{26}ClN_2O_4$  ( $M+H^+$ ): 477.1581, found 477.1584;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 51

3-[2-Methyl-4-(3-[[3-methyl-benzo[b]thiophene-2-carbonyl]-amino]-methyl)-phenoxy]-phenyl]-propionic acid

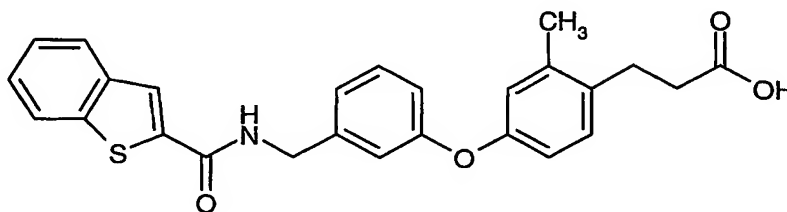


15 The title compound is prepared according to Example 1 utilizing 3-methyl-benzo[b]thiophene-2-carboxylic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{27}H_{26}NO_4S$  ( $M+H^+$ ): 460.1582, found 460.1578;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

20

Example 52

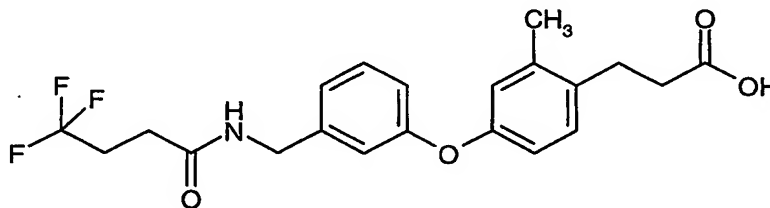
3-[4-(3-[[ (Benzo[b]thiophene-2-carbonyl)-amino]-methyl]-phenoxy)-2-methyl-phenyl]-propionic acid



5           The title compound is prepared according to Example 1 utilizing benzo[b]thiophene-2-carboxylic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{26}H_{24}NO_4S$  ( $M+H^+$ ): 446.1439, found 446.1439;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10           Example 53

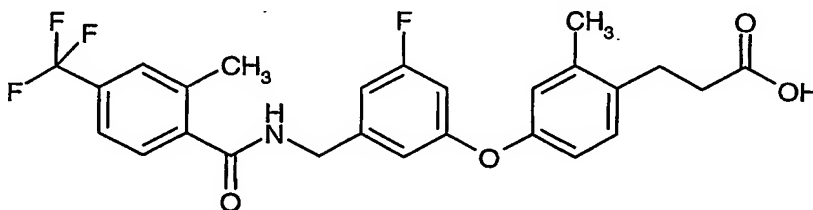
3-(2-Methyl-4-{3-[(4,4,4-trifluoro-butylamino)-methyl]-phenoxy}-phenyl)-propionic acid



15           The title compound is prepared according to Example 1 utilizing 4,4,4-trifluoro-butyl acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{21}H_{23}F_3NO_4$  ( $M+H^+$ ): 410.1579, found 410.1586;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 54

3-(4-{3-Fluoro-5-[(2-methyl-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenyl)-propionic acid

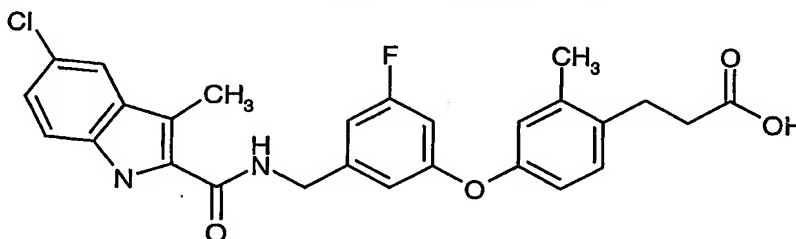


5 The title compound is prepared according to Example 1 utilizing 2-methyl-4-trifluoromethyl-benzoic acid (Intermediate 10) and 3-[4-(3-aminomethyl-5-fluorophenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 36). Exact mass calcd for  $C_{26}H_{24}F_4NO_4$  ( $M+H^+$ ): 490.1641, found 490.1653;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 55

3-[4-(3-{[(5-Chloro-3-methyl-1H-indole-2-carbonyl)-amino]-methyl}-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid



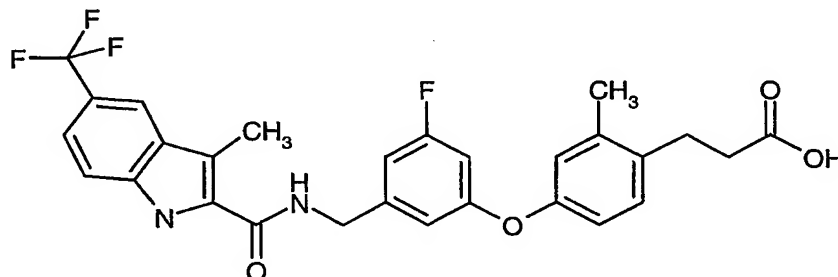
15 The title compound is prepared according to Example 1 utilizing 5-chloro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 3) and 3-[4-(3-aminomethyl-5-fluorophenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 36). Exact mass calcd for  $C_{27}H_{25}ClFN_2O_4$  ( $M+H^+$ ): 495.1487, found 495.1487;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

20



Example 56

3-[4-(3-Fluoro-5-[[[(3-methyl-5-trifluoromethyl-1H-indole-2-carbonyl)-amino]-methyl]-phenoxy)-2-methyl-phenyl]-propionic acid

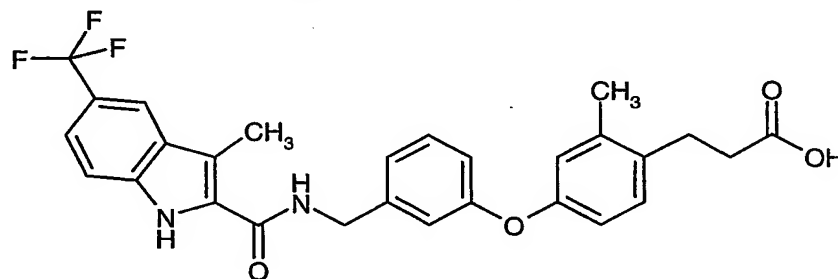


5           The title compound is prepared according to Example 1 utilizing 3-methyl-5-trifluoromethyl-1H-indole-2-carboxylic acid (Intermediate 5) and 3-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 36).  
Exact mass calcd for  $C_{28}H_{25}F_4N_2O_4$  ( $M+H^+$ ): 529.1750, found 529.1757;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 57

3-[2-Methyl-4-(3-[[[(3-methyl-5-trifluoromethyl-1H-indole-2-carbonyl)-amino]-methyl]-phenoxy)-phenyl]-propionic acid

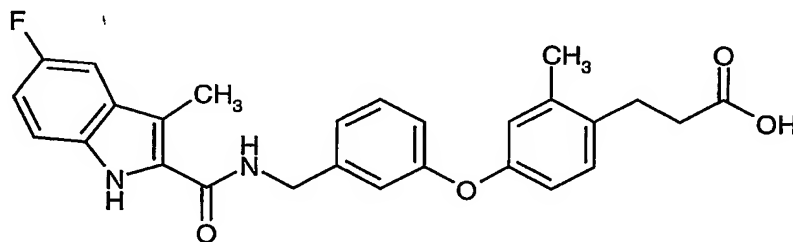


15           The title compound is prepared according to Example 1 utilizing 3-methyl-5-trifluoromethyl-1H-indole-2-carboxylic acid (Intermediate 5) and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{28}H_{26}F_3N_2O_4$  ( $M+H^+$ ): 511.1844, found 511.1834;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

20

Example 58

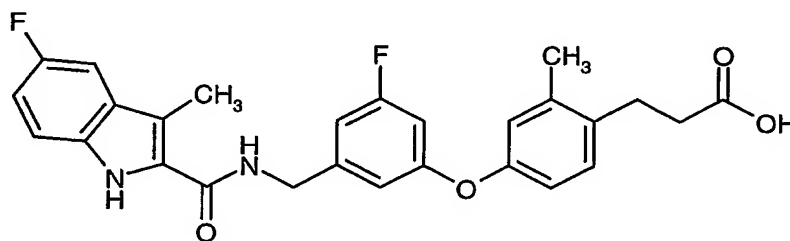
3-[4-(3-[(5-Fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid



The title compound is prepared according to Example 1 utilizing 5-fluoro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 1) and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{27}H_{26}FN_2O_4$  ( $M+H^+$ ): 461.1877, found 461.1873;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 59

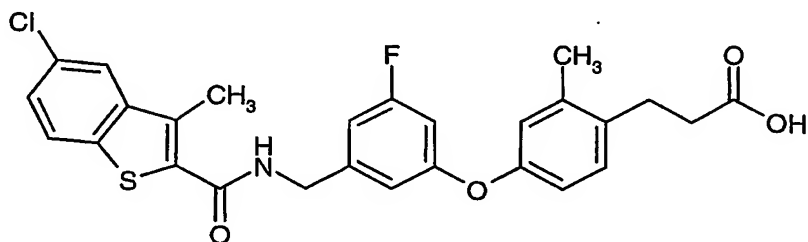
3-[4-(3-Fluoro-5-[(5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid



The title compound is prepared according to Example 1 utilizing 3-methyl-5-trifluoro-1H-indole-2-carboxylic acid (Intermediate 1) and 3-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 36). Exact mass calcd for  $C_{27}H_{25}F_2N_2O_4$  ( $M+H^+$ ): 479.1782, found 479.1787;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 60

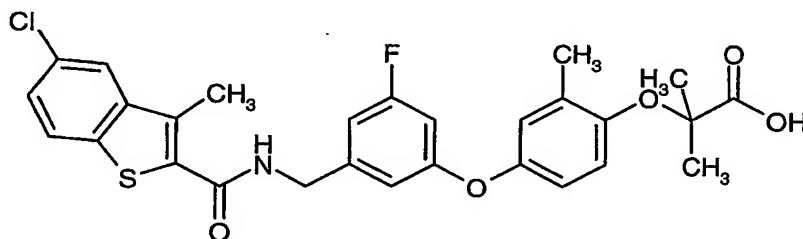
3-[4-(3-[[5-Chloro-3-methyl-benzo[b]thiophene-2-carbonyl]-amino]-methyl)-5-fluorophenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to Example 1 utilizing 5-chloro-3-methyl-benzo[b]thiophene-2-carboxylic acid and 3-[4-(3-aminomethyl-5-fluorophenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 36). Exact mass calcd for  $C_{27}H_{24}ClFNO_4S$  ( $M+H^+$ ): 512.1099, found 512.1160;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 61

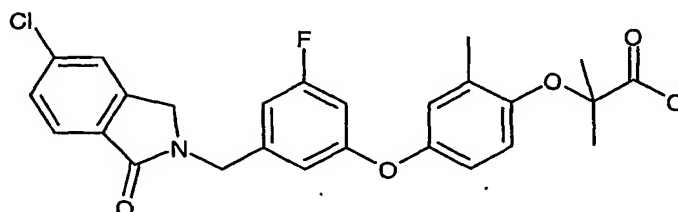
2-[4-(3-[[5-Chloro-3-methyl-benzo[b]thiophene-2-carbonyl]-amino]-methyl)-5-fluorophenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid



The title compound is prepared according to Example 1 utilizing 5-chloro-3-methyl-benzo[b]thiophene-2-carboxylic acid and 2-[4-(3-aminomethyl-5-fluorophenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 47). Exact mass calcd for  $C_{28}H_{26}ClFNO_5S$  ( $M+H^+$ ): 542.1204, found 542.1190;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 62

2-{4-[3-(5-Chloro-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-5-fluoro-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid

Step A

4-chloro-2-methylbenzoic acid methyl ester

4-Chloro-2-methylbenzoic acid (3.4 g, 20.0 mmol) is dissolved in a solution of methanol (25 ml) and dichloromethane (200 ml) and tetramethylsilyl diazomethane (15 mL, 30.0 mmol, 2M in hexane) is added dropwise keeping the temperature near rt with some cooling. Reaction is stirred overnight at rt under nitrogen. Water is added, the organic layer is separated, washed with brine, dried over sodium sulfate and concentrated under reduced pressure providing the title compound with no purification (3.3 g, 90 %). GC/MS:  $M^+$  184;  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ).

Step B

2-Bromomethyl-4-chloro-benzoic acid methyl ester

The compound from Step A (1.0 g, 5.4 mmol), N-bromosuccinimide (1.1 g, 6.0 mmol), and benzoylperoxide (catalytic amount) are refluxed overnight in carbon tetrachloride (10 mL) under nitrogen. Upon cooling the solid is removed by filtration and the filtrate is concentrated under reduced pressure. Ether is added, and the mixture is washed with water and brine, and then dried over sodium sulfate, and concentrated under reduced pressure. The remaining solid is triturated with hexane and collected by filtration providing the title compound (0.65 g, 45 %). GC/MS:  $M^+$  263/264;  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ).

Step C

2-{4-[3-(5-Chloro-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-5-fluoro-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl ester

Compound from Step B (76 mg, 0.29 mmol), 2-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 47) (120 mg, 0.33 mmol), and potassium carbonate (92 mg, 0.66 mmol) are dissolved in dry DMF (10 mL) and stirred at rt overnight under nitrogen. Water is added to the reaction, and the mixture is extracted with ethyl acetate, washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography, eluting with 10 % EtOAc in hexane then 25 % EtOAc in hexane provides the title compound (38 g, 26 %). MS(ES<sup>+</sup>): 512 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

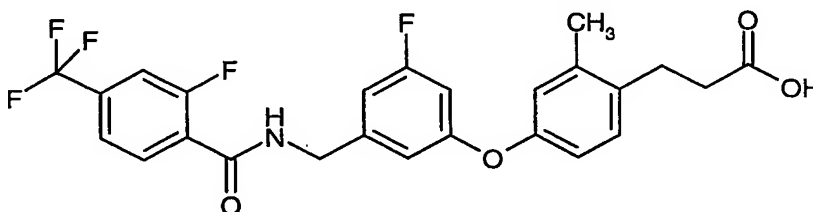
#### Step D

2-{4-[3-(5-Chloro-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-5-fluoro-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid

Compound of Step C (38 mg, 0.074 mmol) is dissolved in dioxane (4 mL) and lithium hydroxide hydrate (40 mg, 0.95 mmol), dissolved in water (2 mL), is added. Mixture is stirred at rt overnight under nitrogen, and then acidified with 5 N HCl. Water is added, and the mixture is extracted with EtOAc, washed with brine, dried over sodium sulfate and concentrated under reduced pressure to give the title compound (36.8 mg, quantitative). Exact mass calculated for C<sub>26</sub>H<sub>24</sub>ClFNO<sub>5</sub> (M+H<sup>+</sup>) 484.1327, found 484.1345; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

#### Example 63

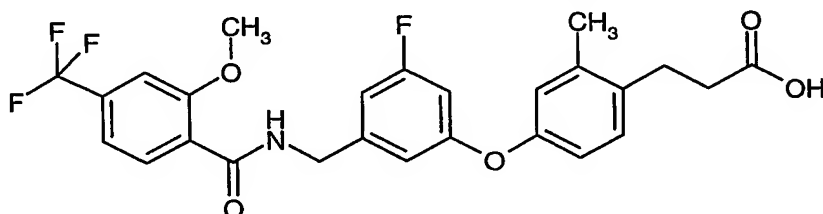
3-(4-{3-Fluoro-5-[(2-fluoro-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenyl)-propionic acid



The title compound is prepared according to Example 1 utilizing 2-fluoro-4-trifluoromethyl-benzoic acid and 3-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 36). Exact mass calcd for C<sub>25</sub>H<sub>21</sub>F<sub>5</sub>NO<sub>4</sub> (M+H<sup>+</sup>): 494.1391, found 494.1379; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Example 64

3-(4-{3-Fluoro-5-[(2-methoxy-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenyl)-propionic acid



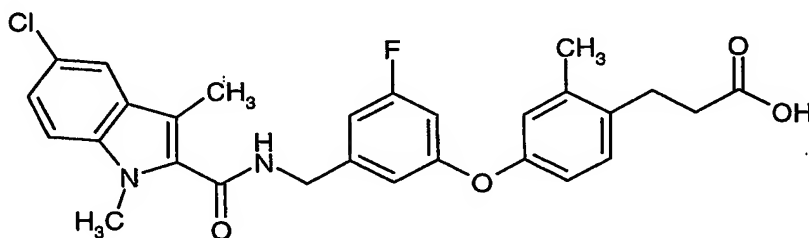
5

The title compound is prepared according to Example 1 utilizing 2-methoxy-4-trifluoromethyl-benzoic acid (*J. Am. Chem. Soc.*; 73; 1951; 2375) and 3-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 36). Exact mass calcd for  $C_{26}H_{24}F_4NO_5$  ( $M+H^+$ ): 506.1591, found 506.1568;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 65

3-[4-(3-{[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl}-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid



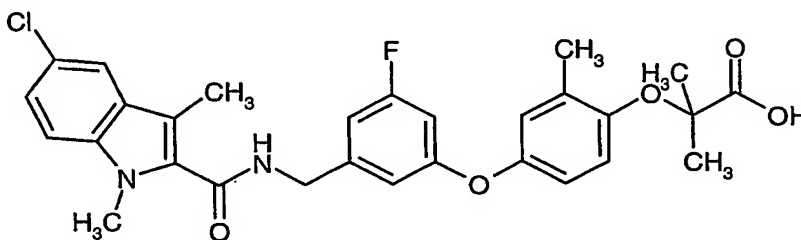
15

The title compound is prepared according to Example 1 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and 3-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 36). Exact mass calcd for  $C_{28}H_{27}ClFN_2O_4$  ( $M+H^+$ ): 509.1643, found 509.1619;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

20

Example 66

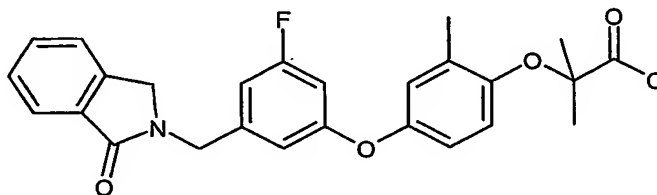
2-[4-(3-[[5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl]-5-fluorophenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid



The title compound is prepared according to Example 1 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and 2-[4-(3-aminomethyl)-5-fluorophenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 47). Exact mass calcd for  $C_{29}H_{29}ClFN_2O_5$  ( $M+H^+$ ): 539.1749, found 539.1733;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 67

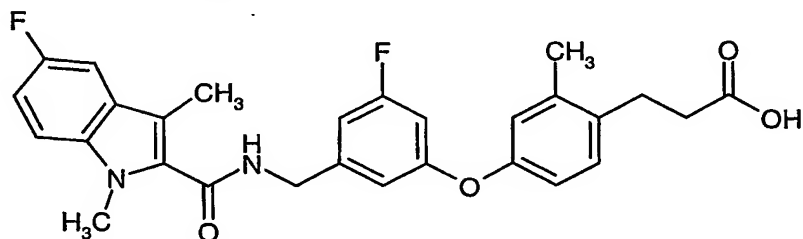
2-[4-[3-Fluoro-5-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-phenoxy]-2-methyl-phenoxy]-2-methyl-propionic acid



The title compound is prepared according to Example 62, Steps C and D, utilizing 2-bromomethyl-benzoic acid and 2-[4-(3-aminomethyl)-5-fluorophenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 47). Exact mass calcd for  $C_{26}H_{25}FNO_5$  ( $M+H^+$ ): 450.1717, found 450.1699;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 68

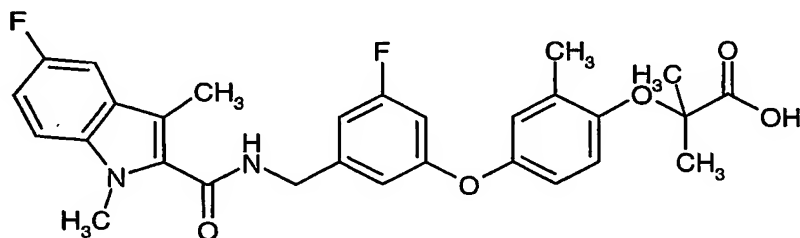
3-[4-(3-Fluoro-5-[[[(5-fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl]-phenoxy]-2-methyl-phenyl]-propionic acid



The title compound is prepared according to Example 1 utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 2) and 3-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 36). Exact mass calcd for  $C_{28}H_{27}F_2N_2O_4$  ( $M+H^+$ ): 493.1939, found 493.1932;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 69

2-[4-(3-Fluoro-5-[[[(5-fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl]-phenoxy]-2-methyl-phenoxy]-2-methyl-propionic acid

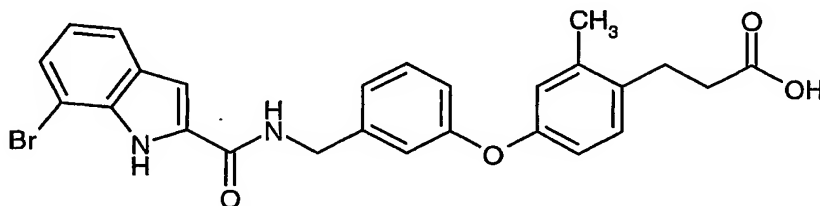


The title compound is prepared according to Example 1 utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 2) and 2-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 47). Exact mass calcd for  $C_{29}H_{29}F_2N_2O_5$  ( $M+H^+$ ): 523.2045, found 523.2038;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).



Example 70

3-[4-(3-[[7-Bromo-1H-indole-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid

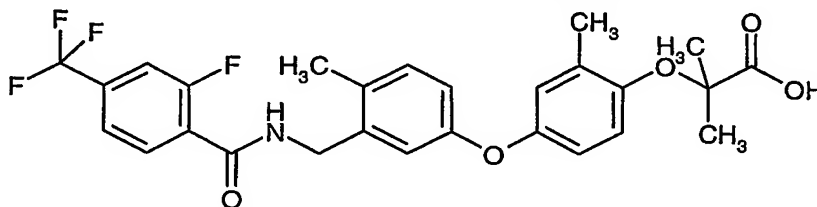


5 The title compound is prepared according to Example 1 utilizing 7-bromo-1H-indole-2-carboxylic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{26}H_{24}BrN_2O_4$  ( $M+H^+$ ): 507.0919, found 507.0929;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 71

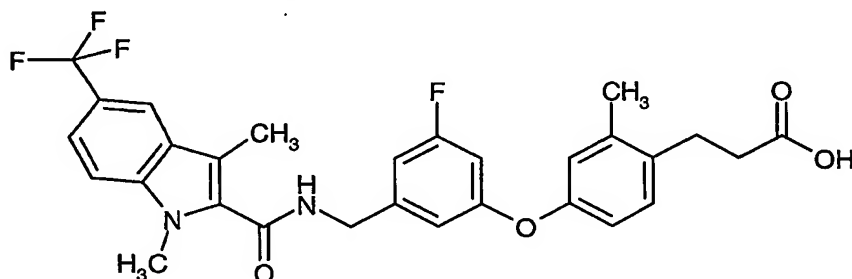
2-(4-{3-[(2-Fluoro-4-trifluoromethyl-benzoylamino)-methyl]-4-methyl-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



15 The title compound is prepared according to Example 1 utilizing 2-fluoro-4-trifluoromethyl-benzoic acid and 2-[4-(3-aminomethyl-4-methyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 19). Exact mass calcd for  $C_{27}H_{26}F_4NO_5$  ( $M+H^+$ ): 520.1747, found 520.1730;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 72

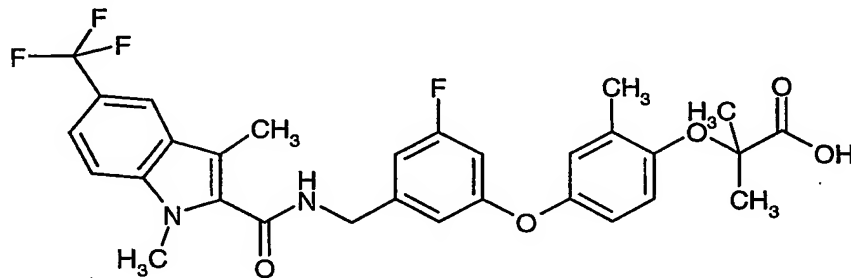
3-[4-(3-[[[(1,3-Dimethyl-5-trifluoromethyl-1H-indole-2-carbonyl)-amino]-methyl]-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to Example 1 utilizing 1,3-dimethyl-5-trifluoromethyl-1H-indole-2-carboxylic acid (Intermediate 6) and 3-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 36). Exact mass calcd for  $C_{29}H_{27}F_4N_2O_4$  ( $M+H^+$ ): 543.1907, found 543.1883;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 73

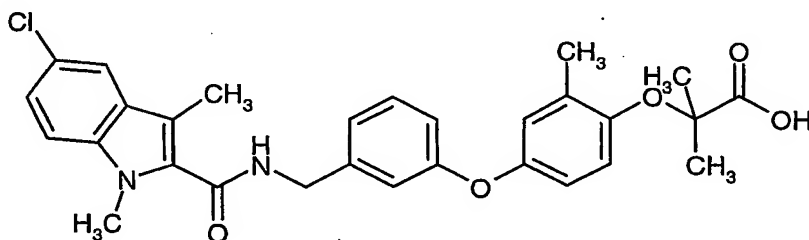
2-[4-(3-[[[(1,3-Dimethyl-5-trifluoromethyl-1H-indole-2-carbonyl)-amino]-methyl]-5-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid



The title compound is prepared according to Example 1 utilizing 1,3-dimethyl-5-trifluoromethyl-1H-indole-2-carboxylic acid (Intermediate 6) and 2-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 47). Exact mass calcd for  $C_{30}H_{29}F_4N_2O_5$  ( $M+H^+$ ): 573.2012, found 573.2009;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 74

2-[4-(3-[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl)-phenoxy]-2-methyl-phenoxy]-2-methyl-propionic acid

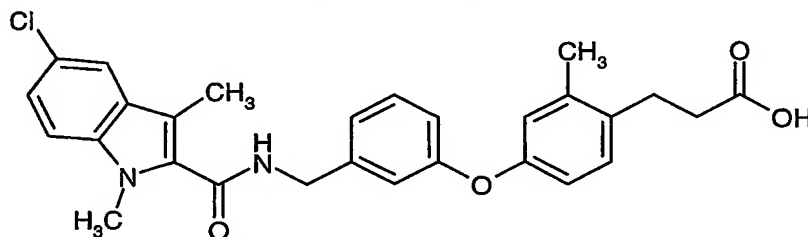


5           The title compound is prepared according to Example 1 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{29}H_{30}ClN_2O_5$  ( $M+H^+$ ): 521.1854, found 521.1843;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 75

3-[4-(3-[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid

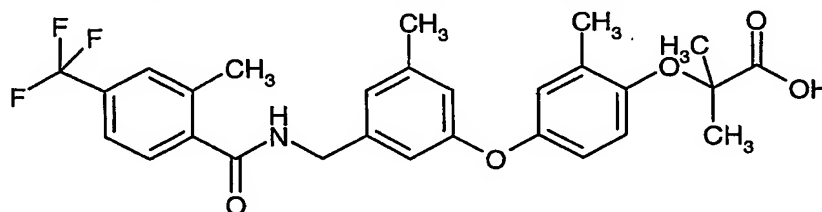


15           The title compound is prepared according to Example 1 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{28}H_{28}ClN_2O_4$  ( $M+H^+$ ): 491.1737, found 491.1731;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

20

Example 76

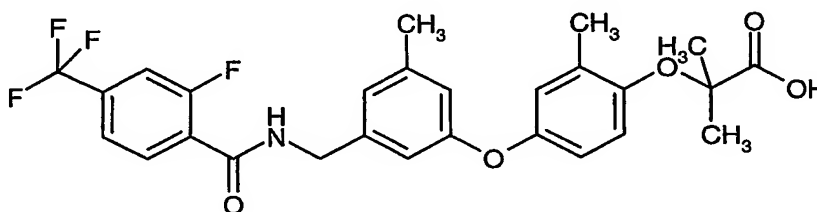
2-Methyl-2-(2-methyl-4-{3-methyl-5-[(2-methyl-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid



The title compound is prepared according to Example 1 utilizing 2-methyl-4-trifluoromethyl-benzoic acid (Intermediate 10) and 2-[4-(3-aminomethyl-5-methyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 20). Exact mass calcd for  $C_{28}H_{29}F_3NO_5$  ( $M+H^+$ ): 516.1998, found 516.2005;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 77

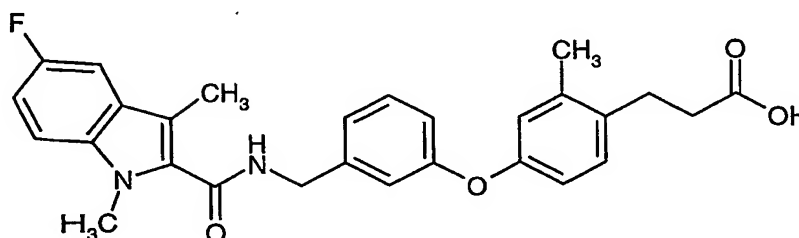
2-(4-{3-[(2-Fluoro-4-trifluoromethyl-benzoylamino)-methyl]-5-methyl-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



The title compound is prepared according to Example 1 utilizing 2-fluoro-4-trifluoromethyl-benzoic acid and 2-[4-(3-aminomethyl-5-methyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 20). Exact mass calcd for  $C_{27}H_{26}F_4NO_5$  ( $M+H^+$ ): 520.1747, found 520.1774;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 78

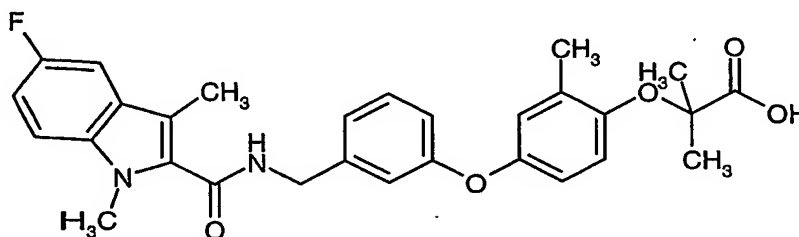
3-[4-(3-{{[(5-Fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl}}-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to Example 1 utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 2) and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{28}H_{28}FN_2O_4$  ( $M+H^+$ ): 475.2033, found 475.2019;  $^1H$  NMR (400 MHz, DMSO-D<sub>6</sub>).

Example 79

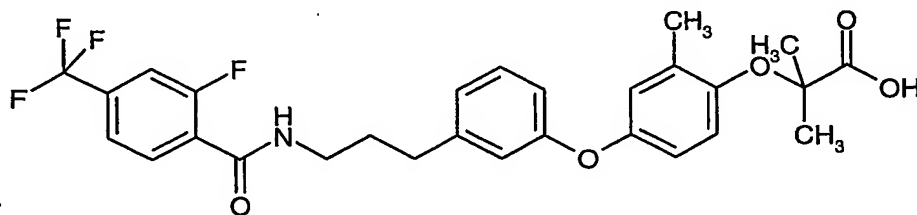
2-[4-(3-{{[(5-Fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl}}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid



The title compound is prepared according to Example 1 utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxyl acid (Intermediate 2) and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{29}H_{30}FN_2O_5$  ( $M+H^+$ ): 505.2139, found 505.2147;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 80

2-(4-{3-[3-(2-Fluoro-4-trifluoromethyl-benzoylamino)-propyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid

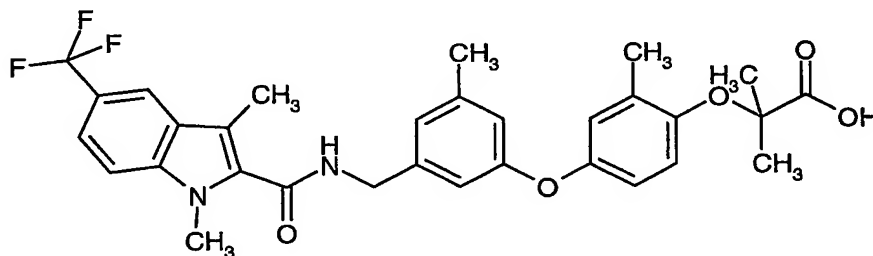


5 The title compound is prepared according to Example 1 utilizing 2-fluoro-4-trifluoromethyl-benzoic acid and 2-{4-[3-(3-amino-propyl)-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl ester (Intermediate 52). Exact mass calcd for  $C_{28}H_{28}F_4NO_5$  ( $M+H^+$ ): 534.1904, found 534.1890;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10.

Example 81

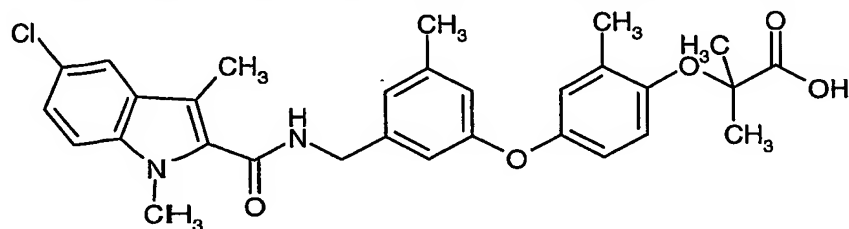
2-[4-(3-{[(1,3-Dimethyl-5-trifluoromethyl-1H-indole-2-carbonyl)-amino]-methyl}-5-methyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid



15 The title compound is prepared according to Example 1 utilizing 1,3-dimethyl-5-trifluoromethyl-1H-indole-2-carboxylic acid (Intermediate 6) and 2-[4-(3-aminomethyl-5-methyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 20). Exact mass calcd for  $C_{31}H_{32}F_3N_2O_5$  ( $M+H^+$ ): 569.2263, found 569.2264;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 82

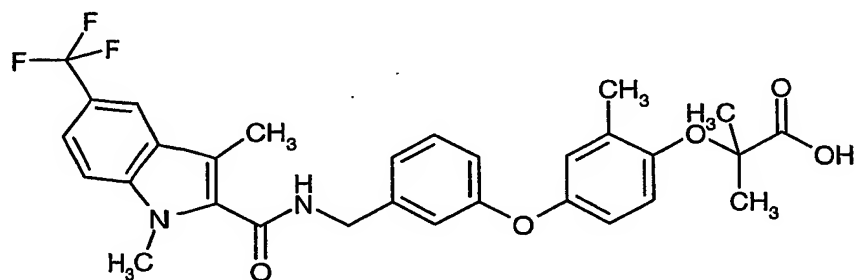
2-[4-(3-[[5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl]-amino]-methyl)-5-methyl-phenoxy]-2-methyl-phenoxy]-2-methyl-propionic acid



The title compound is prepared according to Example 1 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and 2-[4-(3-aminomethyl-5-methyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 20). Exact mass calcd for  $C_{30}H_{32}ClN_2O_5$  ( $M+H^+$ ): 535.200, found 535.1976;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 83

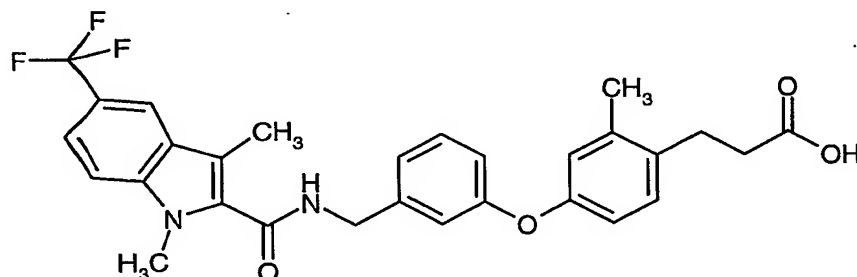
2-[4-(3-[[1,3-Dimethyl-5-trifluoromethyl-1H-indole-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenoxy]-2-methyl-propionic acid



The title compound is prepared according to Example 1 utilizing 1,3-dimethyl-5-trifluoromethyl-1H-indole-2-carboxylic acid (Intermediate 6) and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{30}H_{30}CF_3N_2O_5$  ( $M+H^+$ ): 555.2107, found 555.2088;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 84

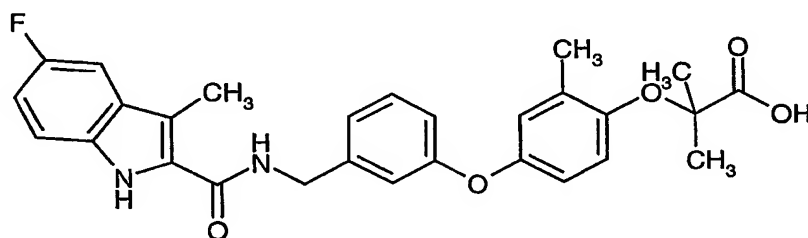
3-[4-(3-[[1,3-Dimethyl-5-trifluoromethyl-1H-indole-2-carbonyl)-amino]-methyl]-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to Example 1 utilizing 1,3-dimethyl-5-trifluoromethyl-1H-indole-2-carboxylic acid (Intermediate 6) and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{29}H_{28}F_3N_2O_4$  ( $M+H^+$ ): 525.2001, found 525.1984;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 85

2-[4-(3-[[5-Fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-methyl]-phenoxy)-2-methyl-phenyl]-propionic acid

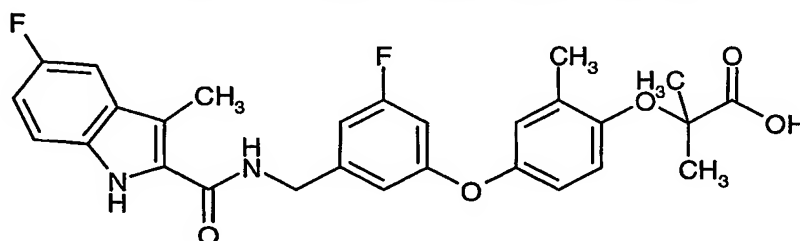


The title compound is prepared according to Example 1 utilizing 5-fluoro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 1) and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{28}H_{28}FN_2O_5$  ( $M+H^+$ ): 491.1982, found 491.1995;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).



Example 86

2-[4-(3-Fluoro-5-[[5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-methyl]-phenoxy)-  
2-methyl-phenoxy]-2-methyl-propionic acid

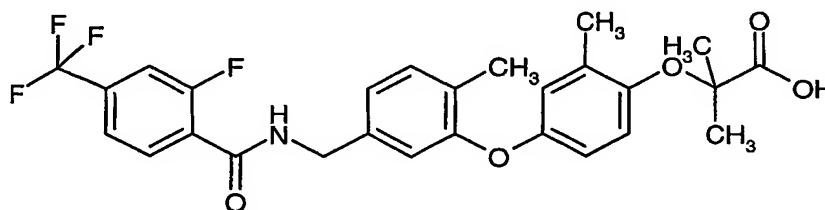


5 The title compound is prepared according to Example 1 utilizing 5-fluoro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 1) and 2-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 47). Exact mass calcd for  $C_{28}H_{27}F_2N_2O_5$  ( $M+H^+$ ): 509.1879, found 509.1888;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 87

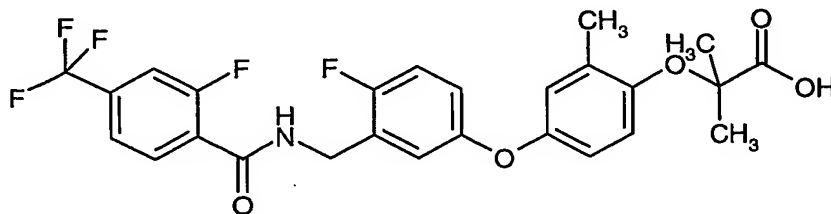
2-(4-{5-[(2-Fluoro-4-trifluoromethyl-benzoylamino)-methyl]-2-methyl-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



15 The title compound is prepared according to Example 1 utilizing 2-fluoro-4-trifluoro-benzoic acid and 2-[4-(5-aminomethyl-2-methyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 21). Exact mass calcd for  $C_{27}H_{26}F_4NO_5$  ( $M+H^+$ ): 520.1747, found 520.1730;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 88

2-(4-{4-Fluoro-3-[(2-fluoro-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid

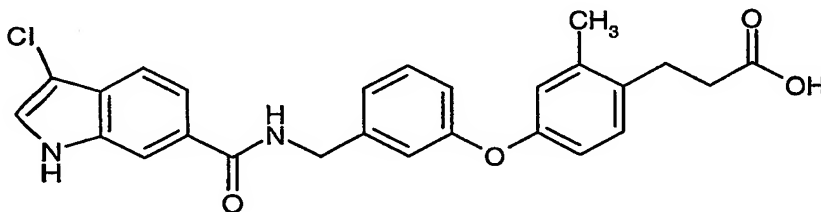


5 The title compound is prepared according to Example 1 utilizing 2-fluoro-4-trifluoro-benzoic acid and 2-[4-(3-aminomethyl-4-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 22). Exact mass calcd for  $C_{26}H_{23}F_5NO_5$  ( $M+H^+$ ): 524.1496, found 524.1494;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 89

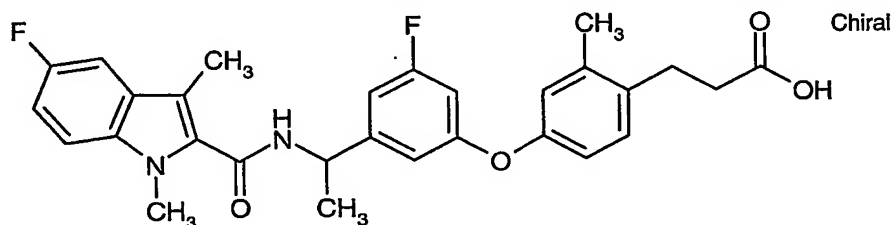
3-[4-(3-{[(3-Chloro-1H-indole-6-carbonyl)-amino]-methyl}-phenoxy)-2-methyl-phenyl]-propionic acid



15 The title compound is prepared according to Example 1 utilizing 3-chloro-1H-indole-6-carboxylic acid (WO 9900128) and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{26}H_{24}ClN_2O_4$  ( $M+H^+$ ): 463.1420, found 463.1425;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 90

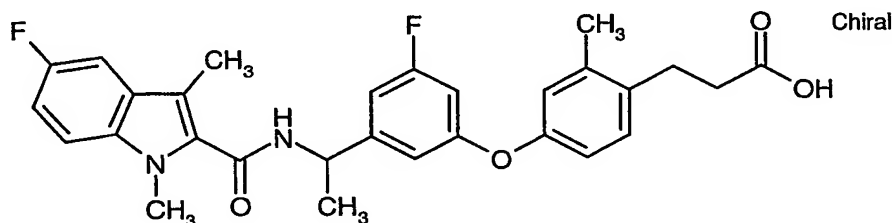
3-[4-(3-Fluoro-5-{1-[(5-fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenyl]-propionic acid, isomer 1



5 The methyl ester of the title compound is prepared according to Example 1, Step A utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 2) and (R, S)-3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (Intermediate 34). Chiral chromatography is used to separate the ester enantiomers. The title compound is then prepared according to Example 1, Step B  
10 utilizing the pure ester enantiomer. Exact mass calcd for  $C_{29}H_{29}F_2N_2O_4$  ( $M+H^+$ ): 507.2095, found 507.2096;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 91

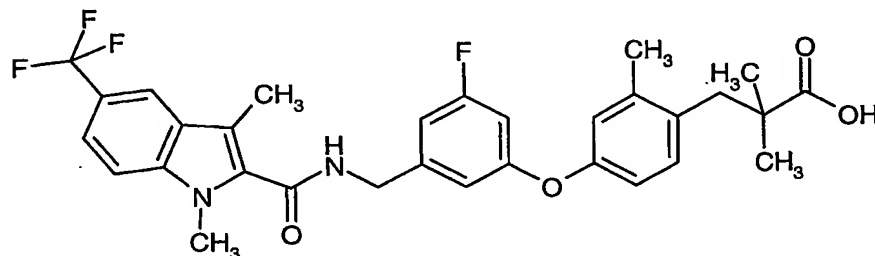
15 3-[4-(3-Fluoro-5-{1-[(5-fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenyl]-propionic acid, isomer 2



The methyl ester of the title compound is prepared according to Example 1, Step A utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 2) and (R, S)-3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid  
20 methyl ester (Intermediate 34). Chiral chromatography is used to separate the ester enantiomers. The title compound is then prepared according to Example 1, Step B utilizing the pure ester enantiomer. Exact mass calcd for  $C_{29}H_{29}F_2N_2O_4$  ( $M+H^+$ ): 507.2095, found 507.2096;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 92

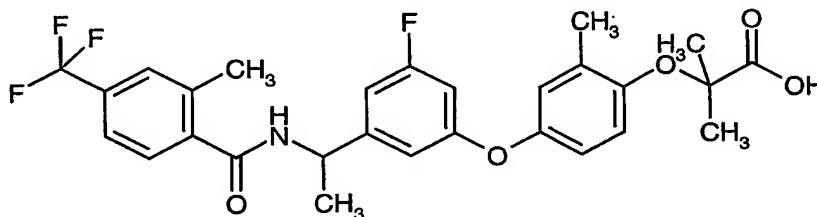
3-[4-(3-{[(1,3-Dimethyl-5-trifluoromethyl-1H-indole-2-carbonyl)-amino]-methyl}-5-fluoro-phenoxy)-2-methyl-phenyl]-2,2-dimethyl-propionic acid



The title compound is prepared according to Example 1 utilizing 1,3-dimethyl-5-trifluoromethyl-1H-indole-2-carboxylic acid (Intermediate 6) and 3-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenyl]-2,2-dimethyl-propionic acid methyl ester (Intermediate 42). Exact mass calcd for  $C_{31}H_{31}F_4N_2O_4$  ( $M+H^+$ ): 571.2220, found 571.2208;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 93

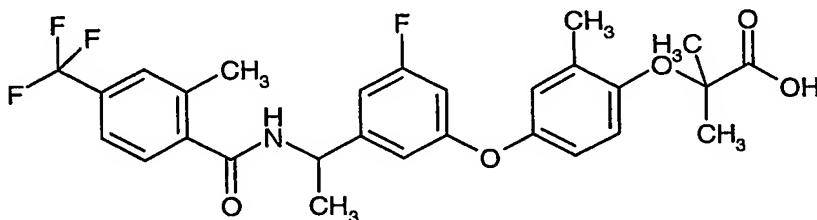
2-(4-{3-Fluoro-5-[1-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid, isomer 1



The methyl ester of the title compound is prepared according to Example 1, Step A utilizing 2-methyl-4-trifluoromethyl-benzoic acid (Intermediate 10) and (R, S)-2-[4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenoxy]-2-methyl-propionic acid methyl ester (Intermediate 41). Chiral chromatography is used to separate the ester enantiomers. The title compound is then prepared according to Example 1, Step B utilizing the pure ester enantiomer. Exact mass calcd for  $C_{28}H_{28}F_4NO_5$  ( $M+H^+$ ): 534.1904, found 534.1887;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 94

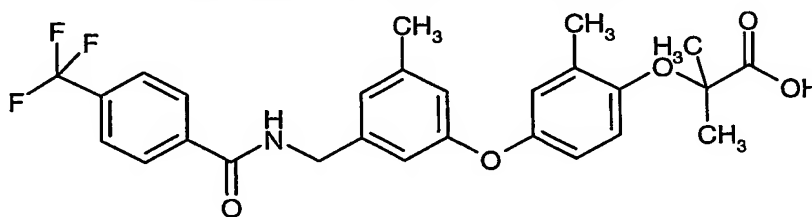
2-(4-{3-Fluoro-5-[1-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid, isomer 2



5 The methyl ester of the title compound is prepared according to Example 1, Step A utilizing 2-methyl-4-trifluoromethyl-benzoic acid (Intermediate 10) and (R, S)-2-[4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenoxy]-2-methyl-propionic acid methyl ester (Intermediate 41). Chiral chromatography is used to separate the ester enantiomers. The title compound is then prepared according to Example 1, Step B  
10 utilizing the pure ester enantiomer. Exact mass calcd for  $C_{28}H_{28}F_4NO_5$  ( $M+H^+$ ): 534.1904, found 534.1884;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 95

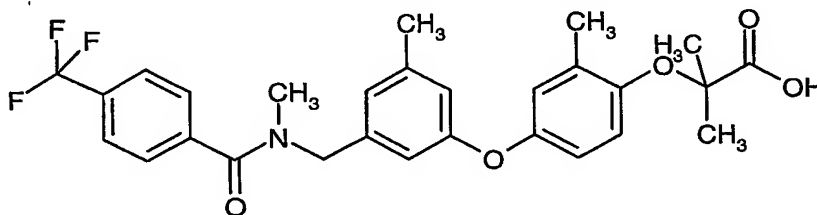
2-Methyl-2-(2-methyl-4-{3-methyl-5-[(4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid



15 The title compound is prepared according to Example 1 utilizing 4-trifluoromethyl-benzoic acid and 2-[4-(3-aminomethyl-5-methyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 20). Exact mass calcd for  $C_{27}H_{27}F_3NO_5$  ( $M+H^+$ ): 502.1841, found 502.1841;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).  
20

Example 96

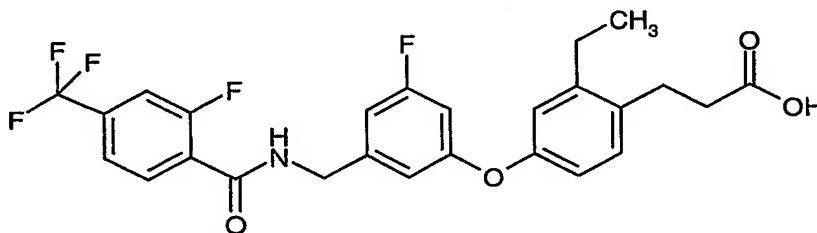
2-Methyl-2-[2-methyl-4-(3-methyl-5-{[methyl-(4-trifluoromethyl-benzoyl)-amino]-methyl}-phenoxy)-phenoxy]-propionic acid



The title compound is prepared according to Intermediate 2, Steps A and B, utilizing 2-methyl-2-(2-methyl-4-{3-methyl-5-[(4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid ethyl ester (Example 95, Step A). Exact mass calcd for  $C_{28}H_{29}F_3NO_5$  ( $M+H^+$ ): 516.1998, found 516.1990;  $^1H$  NMR (400 MHz, DMSO- $D_6$ ).

Example 97

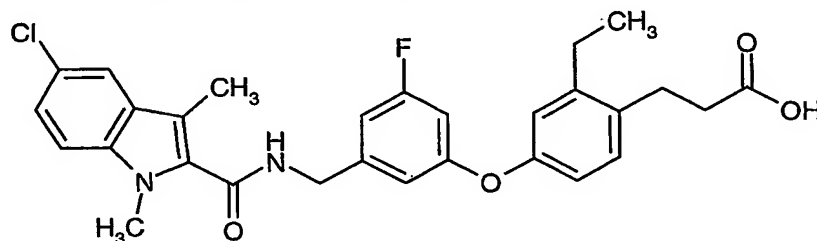
3-(2-Ethyl-4-{3-fluoro-5-[(2-fluoro-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenyl)-propionic acid



The title compound is prepared according to Example 1 utilizing 2-fluoro-5-trifluoromethyl-benzoic acid and 3-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-ethyl-phenyl]-propionic acid ethyl ester (Intermediate 27). Exact mass calcd for  $C_{26}H_{23}F_5NO_4$  ( $M+H^+$ ): 508.1547, found 508.1534;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 98

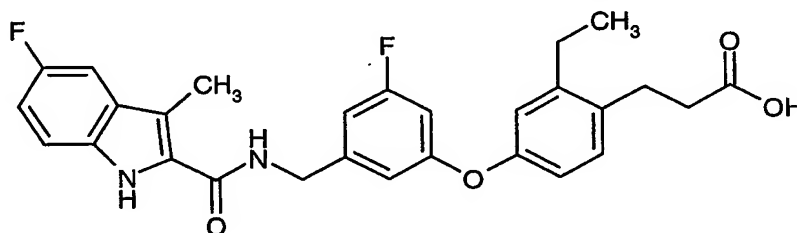
3-[4-(3-[[[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl]-5-fluoro-phenoxy)-2-ethyl-phenyl]-propionic acid



The title compound is prepared according to Example 1 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and 3-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-ethyl-phenyl]-propionic acid ethyl ester (Intermediate 27). Exact mass calcd for  $C_{29}H_{29}ClFN_2O_4$  ( $M+H^+$ ): 523.1800, found 523.1776;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 99

3-[2-Ethyl-4-(3-fluoro-5-[[[(5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-methyl]-phenoxy)-phenyl]-propionic acid

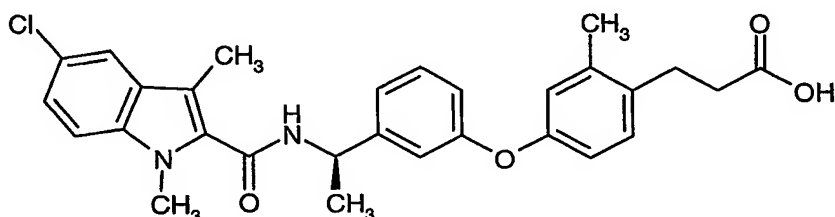


The title compound is prepared according to Example 1 utilizing 5-fluoro-3-methyl-1H-indole-2-carboxylic acid (Example 1) and 3-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-ethyl-phenyl]-propionic acid ethyl ester (Intermediate 27). Exact mass calcd for  $C_{28}H_{27}F_2N_2O_4$  ( $M+H^+$ ): 493.1939, found 493.1942;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 100

(R)-3-[4-(3-{1-[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenyl]-propionic acid

Chiral

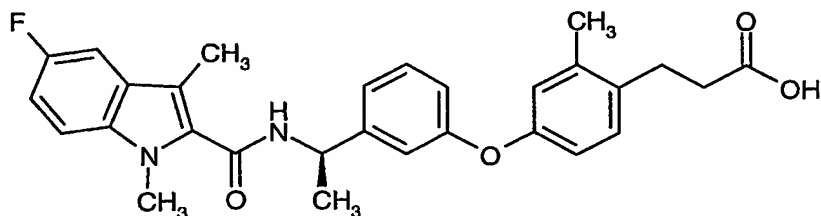


The title compound is prepared according to Example 1 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and (R)-3-{4-[3-(1-amino-ethyl)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (Intermediate 24). Exact mass calcd for  $C_{29}H_{30}ClN_2O_4$  ( $M+H^+$ ): 505.1894, found 505.1909;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 101

(R)-3-[4-(3-{1-[(5-Fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenyl]-propionic acid

Chiral



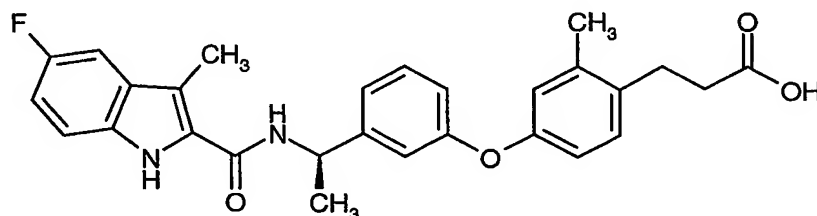
The title compound is prepared according to Example 1 utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 2) and (R)-3-{4-[3-(1-amino-ethyl)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (Intermediate 24). Exact mass calcd for  $C_{29}H_{30}FN_2O_4$  ( $M+H^+$ ): 489.2189, found 489.2190;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).



Example 102

(R)-3-[4-(3-{1-[(5-Fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenyl]-propionic acid

Chiral

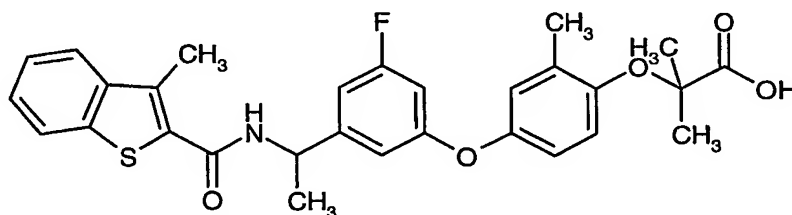


5 The title compound is prepared according to Example 1 utilizing 5-fluoro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 1) and (R)-3-{4-[3-(1-amino-ethyl)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (Intermediate 24). Exact mass calcd for  $C_{28}H_{28}FN_2O_4$  ( $M+H^+$ ): 475.2021, found 475.2033;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 103

2-[4-(3-Fluoro-5-{1-[(3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid, isomer 1

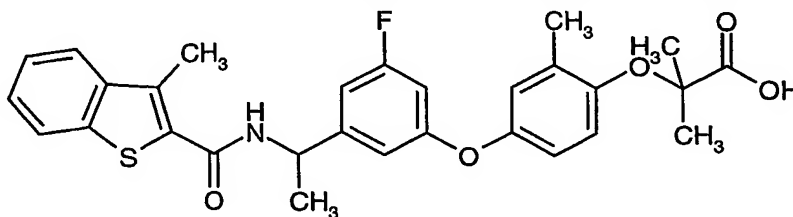


15 The ethyl ester of the title compound is prepared according to Example 1 Step A utilizing 3-methyl-benzo[b]thiophene-2-carboxylic acid and (R, S)-2-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl ester (Intermediate 41). Chiral chromatography is used to separate the ester enantiomers. The title compound is then prepared according to Example 1, Step B utilizing the pure ester enantiomer. Exact mass calcd for  $C_{29}H_{29}FNO_5S$  ( $M+H^+$ ): 522.1750, found 522.1749;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

20

Example 104

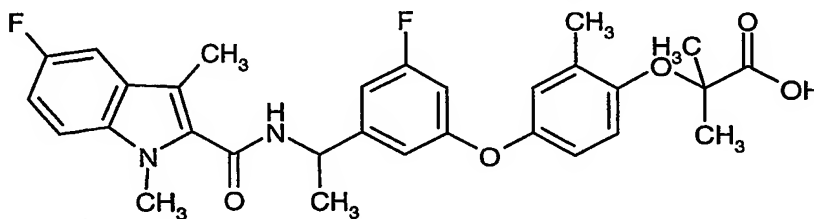
2-[4-(3-Fluoro-5-{1-[(3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid, isomer 2



5 The ethyl ester of the title compound is prepared according to General Procedure, Step A as described in Example 1 by utilizing 3-methyl-benzo[b]thiophene-2-carboxylic acid and (R, S)-2-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl ester (Intermediate 41). Chiral chromatography is used to separate the ester enantiomers. The title compound is then prepared according to Example 1, Step B utilizing the pure ester enantiomer. Exact mass calcd for  $C_{29}H_{29}FNO_5S$  ( $M+H^+$ ): 522.1750, found 522.1749;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 105

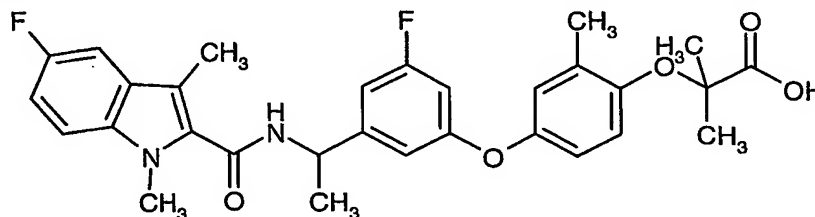
2-[4-(3-Fluoro-5-{1-[(5-fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid, isomer 1



15 The ethyl ester of the title compound is prepared according to Example 1, Step A utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 2) and (R, S)-2-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl ester (Intermediate 41). Chiral chromatography is used to separate the ester enantiomers. The title compound is then prepared according to Example 1, Step B utilizing the pure ester enantiomer. Exact mass calcd for  $C_{30}H_{30}F_2N_2O_5$  ( $M+H^+$ ):, found;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 106

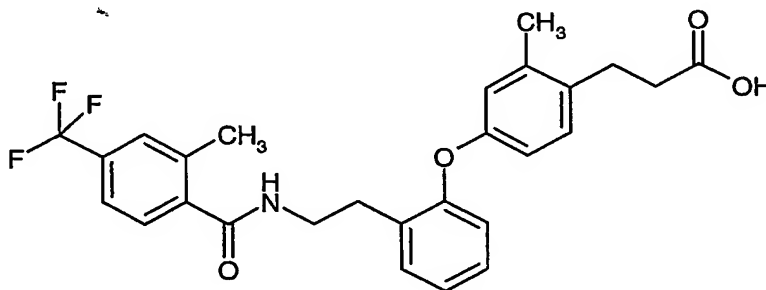
2-[4-(3-Fluoro-5-{1-[(5-fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid, isomer 2



- 5 The ethyl ester of the title compound is prepared according to Example 1, Step A utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 2) and (R, S)-2-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl ester (Intermediate 41). Chiral chromatography is used to separate the ester enantiomers. The title compound is then prepared according to Example 1, Step
- 10 B utilizing the pure ester enantiomer. Exact mass calcd for  $C_{30}H_{30}F_2N_2O_5$  ( $M+H^+$ ): found;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 107

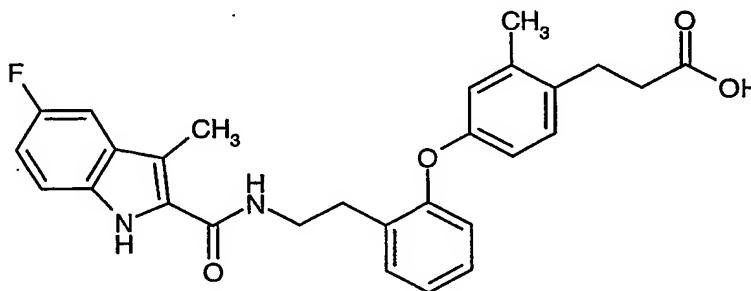
3-(2-Methyl-4-{2-[2-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenyl)-propionic acid



- 15 The title compound is prepared according to Example 1 utilizing 2-methyl-4-trifluoromethyl-benzoic acid (Intermediate 10) and 3-{4-[2-(2-amino-ethyl)-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester (Intermediate 28). Exact mass calcd for
- 20  $C_{27}H_{27}F_3NO_4$  ( $M+H^+$ ): 486.1892, found 486.1893;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 108

3-[4-(2-{2-[(5-Fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenyl]-propionic acid

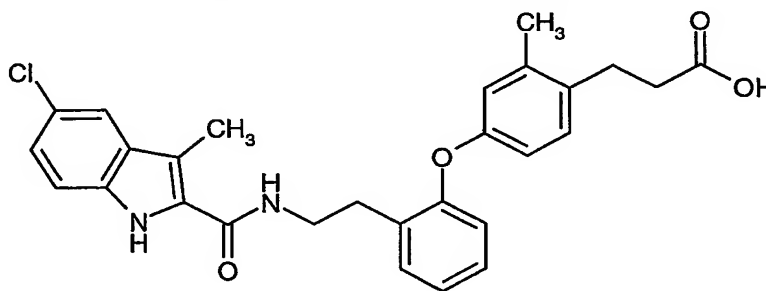


5 The title compound is prepared according to Example 1 utilizing 5-fluoro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 1) and 3-{4-[2-(2-amino-ethyl)-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester (Intermediate 28). Exact mass calcd for  $C_{28}H_{28}FN_2O_4$  ( $M+H^+$ ): 475.2033, found 475.2015;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 109

3-[4-(2-{2-[(5-Chloro-3-methyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenyl]-propionic acid

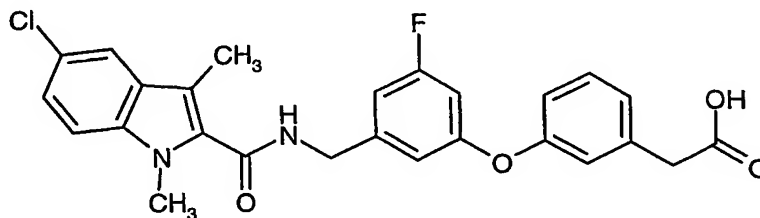


15 The title compound is prepared according to Example 1 utilizing 5-chloro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 3) and 3-{4-[2-(2-amino-ethyl)-phenoxy]-2-methyl-phenyl}-propionic acid ethyl ester (Intermediate 28). Exact mass calcd for  $C_{28}H_{28}ClN_2O_4$  ( $M+H^+$ ): 491.1737, found 491.1724;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

20

Example 110

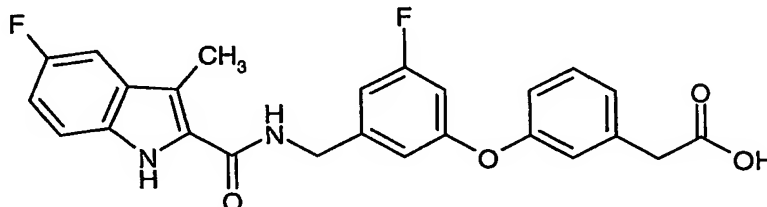
[3-(3-[[[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl]-5-fluoro-phenoxy]-phenyl]-acetic acid



The title compound is prepared according to Example 1 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and [3-(3-aminomethyl-5-fluoro-phenoxy)-phenyl]-acetic acid methyl ester (Intermediate 48). Exact mass calcd for  $C_{26}H_{23}ClFN_2O_4$  ( $M+H^+$ ): 481.1330, found 481.1327;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 111

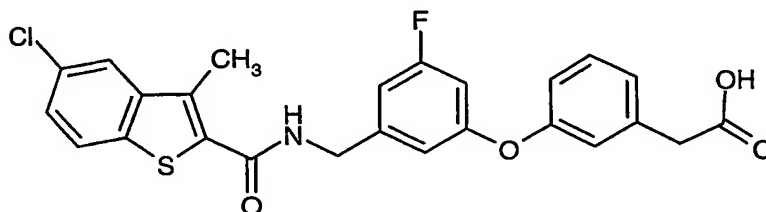
[3-(3-Fluoro-5-[[[(5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-methyl]-phenoxy]-phenyl]-acetic acid



The title compound is prepared according to Example 1 utilizing 5-fluoro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 1) and [3-(3-aminomethyl-5-fluoro-phenoxy)-phenyl]-acetic acid methyl (Intermediate 48). Exact mass calcd for  $C_{25}H_{21}F_2N_2O_4$  ( $M+H^+$ ): 451.1469, found 451.1478;  $^1H$  NMR (400 MHz,  $DMSO-D_6$ ).

Example 112

[3-(3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-methyl)-5-fluorophenoxy)-phenyl]-acetic acid

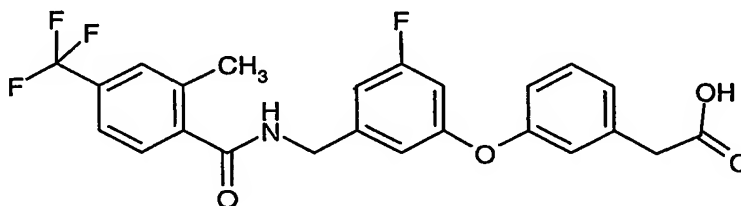


5 The title compound is prepared according to Example 1 utilizing 5-chloro-3-methyl-benzo[b]thiophene-2-carboxylic acid and [3-(3-aminomethyl-5-fluorophenoxy)-phenyl]-acetic acid methyl ester (Intermediate 48). Exact mass calcd for  $C_{25}H_{20}ClFNO_4S$  ( $M+H^+$ ): 484.0786, found 484.0778;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 113

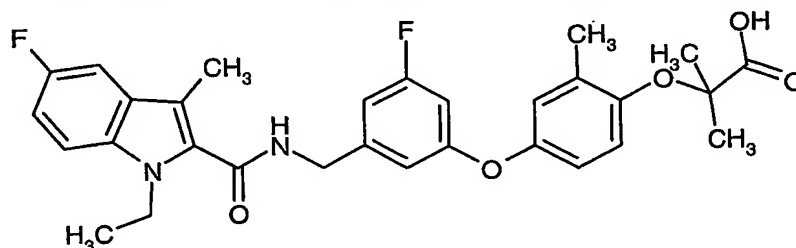
(3-{3-Fluoro-5-[(2-methyl-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenyl)-acetic acid



15 The title compound is prepared according to Example 1 utilizing 3-methyl-5-trifluoromethyl-benzoic acid (Intermediate 10) and [3-(3-aminomethyl-5-fluorophenoxy)-phenyl]-acetic acid methyl ester (Intermediate 48). Exact mass calcd for  $C_{24}H_{20}F_4NO_4$  ( $M+H^+$ ): 462.1332, found 462.1328;  $^1H$  NMR (400 MHz,  $DMSO-D_6$ ).

Example 114

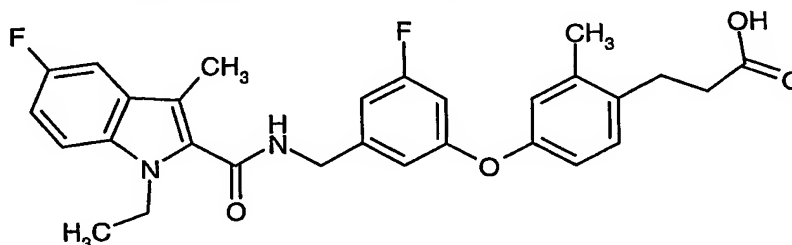
2-[4-(3-[[[(1-Ethyl-5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-methyl]-5-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid



The title compound is prepared according to Example 1 utilizing 1-ethyl-5-fluoro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 9) and 2-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid (Intermediate 47). Exact mass calcd for  $C_{30}H_{31}F_2N_2O_5$  ( $M+H^+$ ): 537.2201, found 537.2215;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 115

3-[4-(3-[[[(1-Ethyl-5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-methyl]-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid

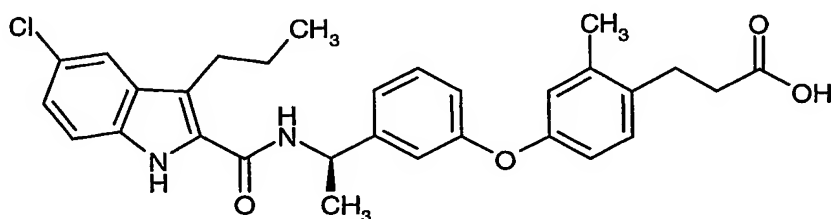


The title compound is prepared according to Example 1 utilizing 1-ethyl-5-fluoro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 9) and 3-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 36). Exact mass calcd for  $C_{29}H_{29}F_2N_2O_4$  ( $M+H^+$ ): 507.2095, found 507.2096;  $^1H$  NMR (400 MHz, DMSO- $D_6$ ).

Example 116

(R)-3-[4-(3-{1-[(5-Chloro-3-propyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenyl]-propionic acid

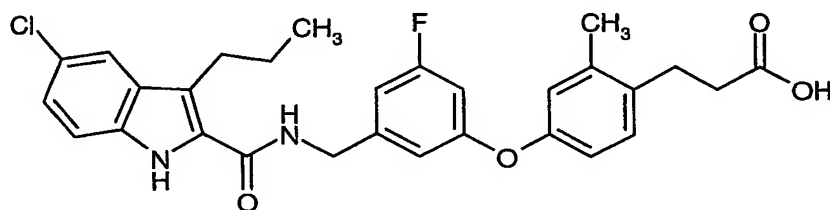
Chiral



The title compound is prepared according to Example 1 utilizing 5-chloro-3-propyl-1H-indole-2-carboxylic acid (Intermediate 7) and (R)-3-[4-[3-(1-amino-ethyl)-phenoxy]-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 24). Exact mass calcd for  $C_{30}H_{32}ClN_2O_4$  ( $M+H^+$ ): 519.2051, found 519.2038;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 117

3-[4-(3-{[(5-Chloro-3-propyl-1H-indole-2-carbonyl)-amino]-methyl}-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid

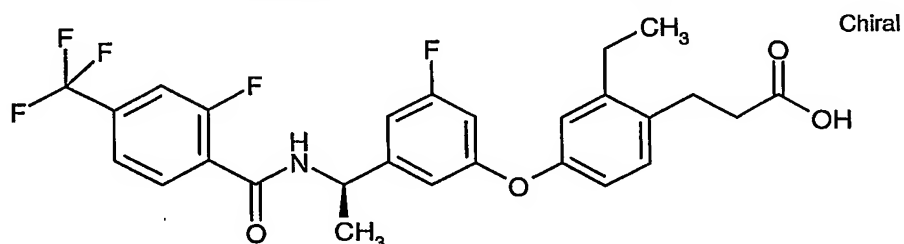


The title compound is prepared according to Example 1 utilizing 5-chloro-3-propyl-1H-indole-2-carboxylic acid (Intermediate 7) and 3-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 36). Exact mass calcd for  $C_{29}H_{29}ClFN_2O_4$  ( $M+H^+$ ): 523.1800, found 523.1810;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).



Example 118

(R)-3-(2-Ethyl-4-{3-fluoro-5-[1-(2-fluoro-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenyl)-propionic acid

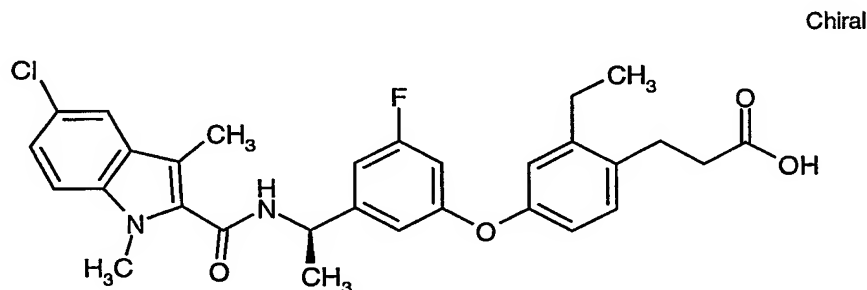


5 The title compound is prepared according to Example 1 utilizing 2-fluoro-5-trifluoromethyl-benzoic acid and (R)-3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester (Intermediate 23). Exact mass calcd for  $C_{27}H_{25}F_5NO_4$  ( $M+H^+$ ): 522.1703, found 522.1686;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 119

(R)-3-[4-(3-{1-[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-fluoro-phenoxy)-2-ethyl-phenyl]-propionic acid



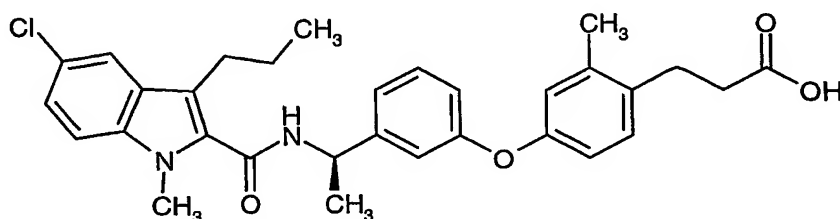
15 The title compound is prepared according to Example 1 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and (R)-3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester (Intermediate 23). Exact mass calcd for  $C_{30}H_{31}ClFN_2O_4$  ( $M+H^+$ ): 537.1956, found 537.1956;  $^1H$  NMR (400 MHz, DMSO- $D_6$ ).

20

Example 120

(R)-3-[4-(3-{1-[(5-Chloro-1-methyl-3-propyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenyl]-propionic acid

Chiral

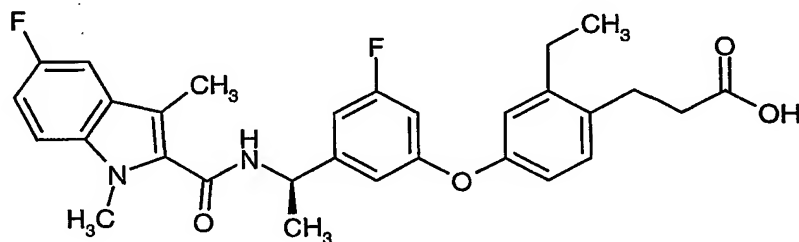


The title compound is prepared according to Example 1 utilizing 5-chloro-1-methyl-3-propyl-1H-indole-2-carboxylic acid (Intermediate 8) and (R)-3-{4-[3-(1-amino-ethyl)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (Intermediate 24). Exact mass calcd for  $C_{31}H_{34}ClN_2O_4$  ( $M+H^+$ ): 533.2207, found 533.2197;  $^1H$  NMR (400 MHz, DMSO- $D_6$ ).

Example 121

(R)-3-[2-Ethyl-4-(3-fluoro-5-{1-[(5-fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-phenyl]-propionic acid

Chiral

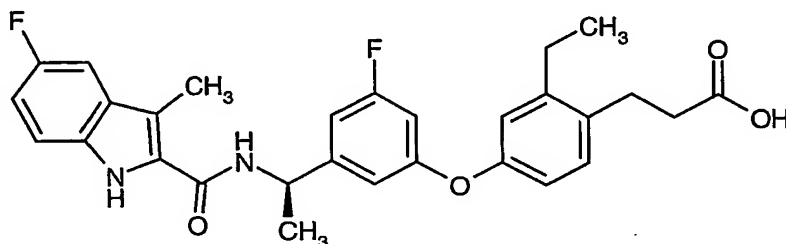


The title compound is prepared according to Example 1 utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 2) and (R)-3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester (Intermediate 23). Exact mass calcd for  $C_{30}H_{31}F_2N_2O_4$  ( $M+H^+$ ): 521.2252, found 521.2236;  $^1H$  NMR (400 MHz, DMSO- $D_6$ ).

Example 122

(R)-3-[2-Ethyl-4-(3-fluoro-5-{1-[(5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-phenyl]-propionic acid

Chiral



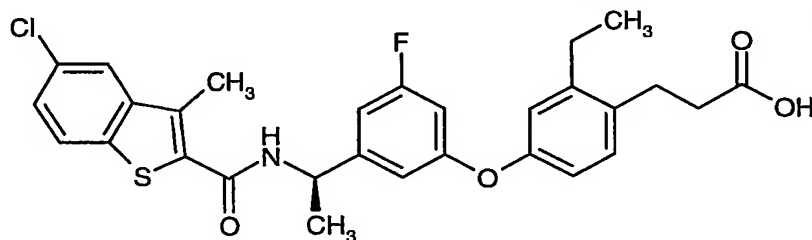
5 The title compound is prepared according to Example 1 utilizing 3-methyl-5-fluoro-1H-indole-2-carboxylic acid (Intermediate 1) and (R)-3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester (Intermediate 23). Exact mass calcd for  $C_{29}H_{29}F_2N_2O_4$  ( $M+H^+$ ): 507.2095, found 507.2087;  $^1H$  NMR (400 MHz, DMSO- $D_6$ ).

10

Example 123

(R)-3-[2-Ethyl-4-(3-fluoro-5-{1-[(5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-phenyl]-propionic acid

Chiral



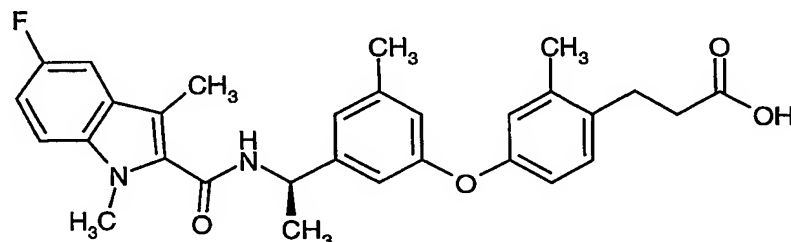
15 The title compound is prepared according to Example 1 utilizing 5-chloro-3-methyl-benzo[b]thiophene-2-carboxylic acid and (R)-3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester (Intermediate 23). Exact mass calcd for  $C_{29}H_{28}ClFNO_4S$  ( $M+H^+$ ): 540.1412, found 540.1439;  $^1H$  NMR (400 MHz, DMSO- $D_6$ ).

20

Example 124

(R)-3-[4-(3-{1-[(5-Fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid

Chiral



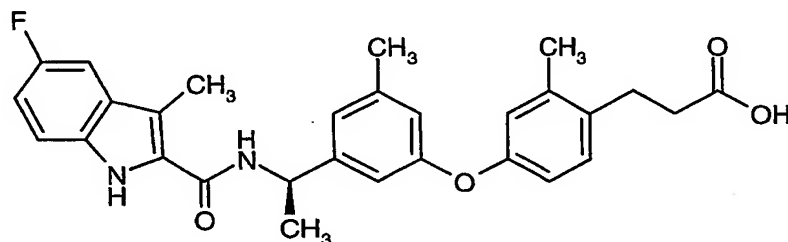
5 The title compound is prepared according to Example 1 utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 2) and (R)-3-{4-[3-(1-amino-ethyl)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (Intermediate 26). Exact mass calcd for  $C_{30}H_{32}FN_2O_4$  ( $M+H^+$ ): 518.1954, found 518.1956;  $^1H$  NMR (400 MHz, DMSO- $D_6$ ).

10

Example 125

(R)-3-[4-(3-{1-[(5-Fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid

Chiral



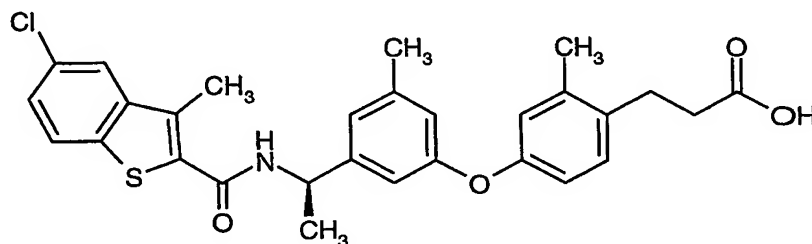
15 The title compound is prepared according to Example 1 utilizing 5-fluoro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 1) and (R)-3-{4-[3-(1-amino-ethyl)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (Intermediate 26). Exact mass calcd for  $C_{29}H_{30}FN_2O_4$  ( $M+H^+$ ): 489.2190, found 489.2169;  $^1H$  NMR (400 MHz, DMSO- $D_6$ ).

20

Example 126

(R)-3-[4-(3-{1-[(5-Chloro-3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-ethyl}-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid

Chiral



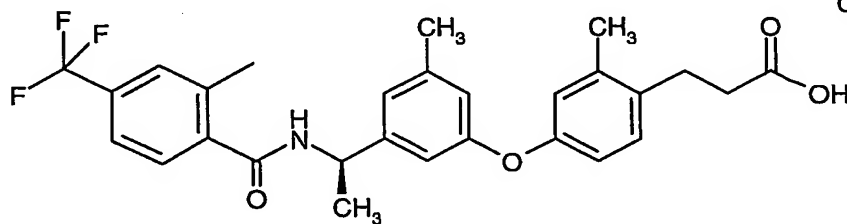
5 The title compound is prepared according to Example 1 utilizing 5-chloro-3-methyl-benzo[b]thiophene-2-carboxylic acid and (R)-3-{4-[3-(1-amino-ethyl)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (Intermediate 26). Exact mass calcd for  $C_{29}H_{29}ClNO_4S$  ( $M+H^+$ ): 522.1506, found 522.1501;  $^1H$  NMR (400 MHz, DMSO- $D_6$ ).

10

Example 127

(R)-3-(2-Methyl-4-{3-methyl-5-[1-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenyl)-propionic acid

Chiral



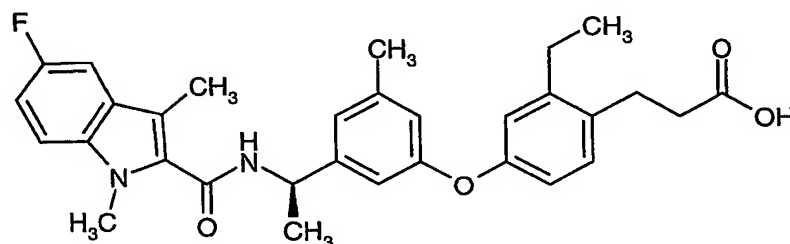
15 The title compound is prepared according to Example 1 utilizing 2-methyl-5-trifluoromethyl-benzoic acid (Intermediate 10) and (R)-3-{4-[3-(1-amino-ethyl)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (Intermediate 26). Exact mass calcd for  $C_{28}H_{29}F_3NO_4$  ( $M+H^+$ ): 500.2049, found 500.2016;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

20

Example 128

(R)-3-[2-Ethyl-4-(3-{1-[(5-fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-methyl-phenoxy)-phenyl]-propionic acid

Chiral



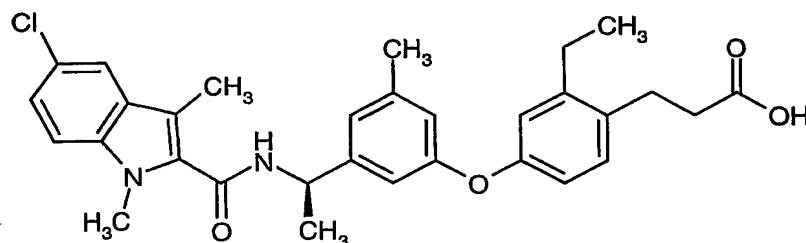
5 The title compound is prepared according to Example 1 utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 2) and (R)-3-{4-[3-(1-amino-ethyl)-5-methyl-phenoxy]-2-ethyl-phenyl}-propionic acid methyl ester (Intermediate 16). Exact mass calcd for  $C_{31}H_{34}FN_2O_4$  ( $M+H^+$ ): 517.2502, found 517.2493;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 129

(R)-3-[4-(3-{1-[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-methyl-phenoxy)-2-ethyl-phenyl]-propionic acid

Chiral

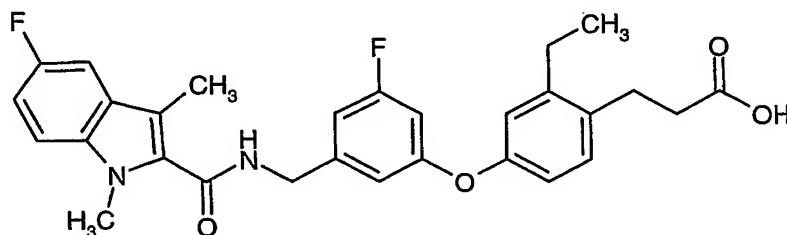


15 The title compound is prepared according to Example 1 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and (R)-3-{4-[3-(1-amino-ethyl)-5-methyl-phenoxy]-2-ethyl-phenyl}-propionic acid (Intermediate 16). Exact mass calcd for  $C_{31}H_{34}ClN_2O_4$  ( $M+H^+$ ): 533.2207, found 533.2222;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

20

Example 130

3-[2-Ethyl-4-(3-fluoro-5-[(5-fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl)-phenoxy)-phenyl]-propionic acid

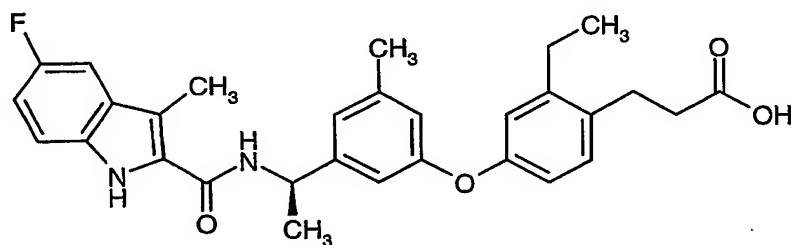


The title compound is prepared according to Example 1 utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 2) and 3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester (Intermediate 27). Exact mass calcd for  $C_{29}H_{29}F_2N_2O_4$  ( $M+H^+$ ): 507.2095, found 507.2101;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 131

(R)-3-[2-Ethyl-4-(3-{1-[(5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-methyl-phenoxy)-phenyl]-propionic acid

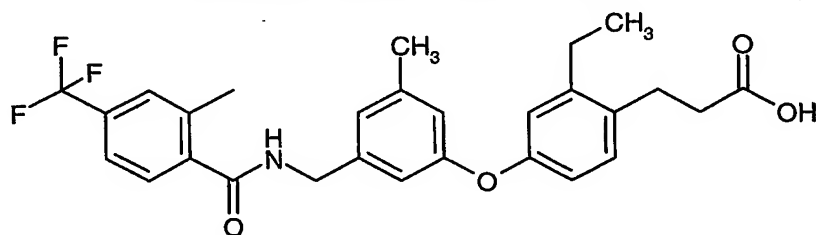
Chiral



The title compound is prepared according to Example 1 utilizing 5-fluoro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 1) and (R)-3-{4-[3-(1-amino-ethyl)-5-methyl-phenoxy]-2-ethyl-phenyl}-propionic acid (Intermediate 16). Exact mass calcd for  $C_{30}H_{32}FN_2O_4$  ( $M+H^+$ ): 503.2346, found 503.2351;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Example 132

3-(2-Ethyl-4-{3-methyl-5-[(2-methyl-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenyl)-propionic acid

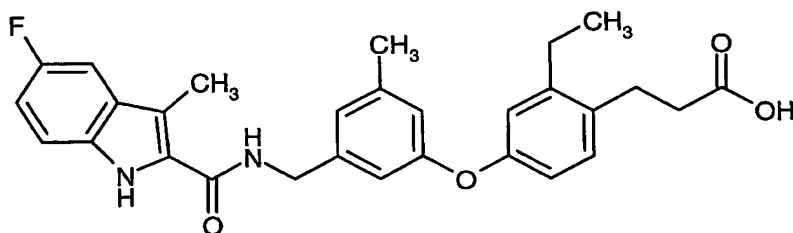


5 The title compound is prepared according to Example 1 utilizing 2-methyl-4-trifluoromethyl-benzoic acid (Intermediate 10) and 3-[4-(3-aminomethyl-5-methyl-phenoxy)-2-ethyl-phenyl]-propionic acid ethyl ester (Intermediate 46). Exact mass calcd for  $C_{28}H_{29}F_3NO_4$  ( $M+H^+$ ): 500.2049, found 500.2048;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

10

Example 133

3-[2-Ethyl-4-(3-[(5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-methyl)-5-methyl-phenoxy]-phenyl]-propionic acid



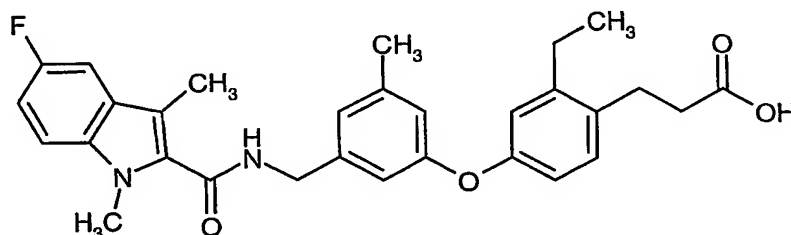
15 The title compound is prepared according to Example 1 utilizing 5-fluoro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 1) and 3-[4-(3-aminomethyl-5-methyl-phenoxy)-2-ethyl-phenyl]-propionic acid ethyl ester (Intermediate 46). Exact mass calcd for  $C_{29}H_{30}FN_2O_4$  ( $M+H^+$ ): 489.2190, found 489.2174;  $^1H$  NMR (400 MHz, DMSO- $D_6$ ).

20



Example 134

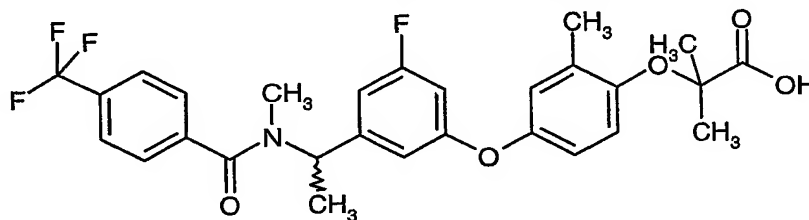
3-[2-Ethyl-4-(3-[[5-fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl}-5-methyl-phenoxy)-phenyl]-propionic acid



The title compound is prepared according to Example 1 utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 2 ) and 3-[4-(3-aminomethyl-5-methyl-phenoxy)-2-ethyl-phenyl]-propionic acid ethyl ester (Intermediate 46). Exact mass calcd for  $C_{30}H_{32}FN_2O_4$  ( $M+H^+$ ): 503.2643, found 503.2326;  $^1H$  NMR (400 MHz, DMSO-D6).

Example 135

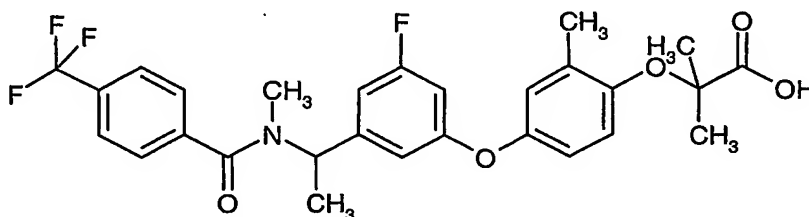
(R,S)-2-[4-(3-Fluoro-5-{1-[methyl-(4-trifluoromethyl-benzoyl)-amino]-ethyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid



The ethyl ester of the title compound is prepared according to Example 1 Step A utilizing 4-trifluoromethyl-benzoic and (R, S)-2-{4-[3-(1-amino-ethyl)-5-fluorophenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl ester (Intermediate 41). The ester is then reacted with sodium hydride according to Intermediate 2, Step A, followed by hydrolysis according to Example 1 Step B providing the title compound. Exact mass calcd for  $C_{28}H_{28}F_4NO_5$  ( $M+H^+$ ): 534.1904, found 534.1910;  $^1H$  NMR (400 MHz, DMSO-D6).

Example 136

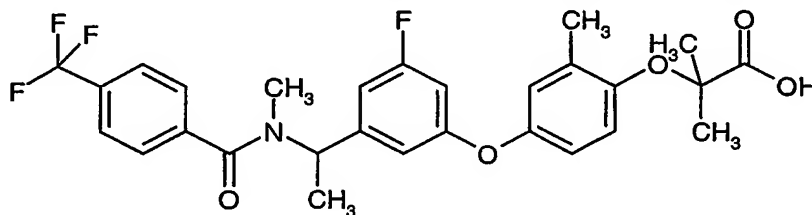
2-[4-(3-Fluoro-5-{1-[methyl-(4-trifluoromethyl-benzoyl)-amino]-ethyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid, isomer 1



- 5 The title compound is prepared utilizing (R,S)-2-[4-(3-Fluoro-5-{1-[methyl-(4-trifluoromethyl-benzoyl)-amino]-ethyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Example 135). Chiral chromatography is used to separate the enantiomers as the esters. The title compound is then prepared according to Example 1, Step B utilizing the pure ester enantiomer. Exact mass calcd for
- 10  $C_{28}H_{28}F_4NO_5$  ( $M+H^+$ ): 534.1904, found 534.1890;  $^1H$  NMR (400 MHz, DMSO- $D_6$ ).

Example 137

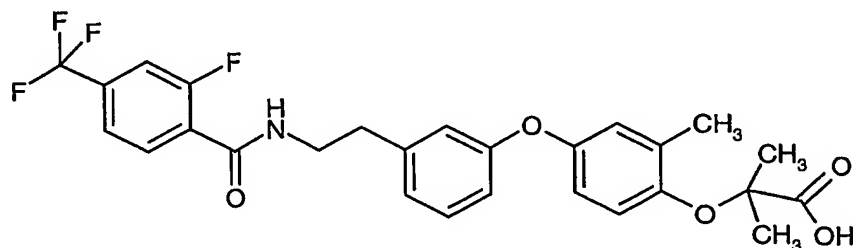
2-[4-(3-Fluoro-5-{1-[methyl-(4-trifluoromethyl-benzoyl)-amino]-ethyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid, isomer 2



- 15 The title compound is prepared utilizing (R,S)-2-[4-(3-Fluoro-5-{1-[methyl-(4-trifluoromethyl-benzoyl)-amino]-ethyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Example 135). Chiral chromatography is used to separate the enantiomers as the esters. The title compound is then prepared according to Example 1, Step B utilizing the pure ester enantiomer. Exact mass calcd for
- 20  $C_{28}H_{28}F_4NO_5$  ( $M+H^+$ ): 534.1904, found 534.1899;  $^1H$  NMR (400 MHz, DMSO- $D_6$ ).

Example 138

2-(4-{3-[2-(2-Fluoro-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid

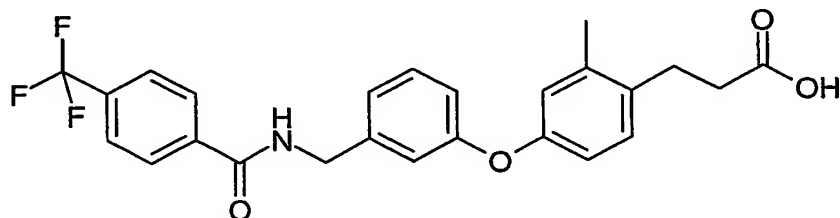


5 The title compound is prepared according to Example 1 utilizing 2-fluoro-4-trifluoromethyl-benzoic acid and 2-{4-[3-(2-amino-ethyl)-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl ester (Intermediate 29). Exact mass calcd for  $C_{27}H_{26}F_4NO_5$  ( $M+NH_4^+$ ): 537.2013, found 537.2028;  $^1H$  NMR (400 MHz, DMSO- $D_6$ ).

10

Example 139

3-(2-Methyl-4-{3-[(4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenyl)-propionic acid

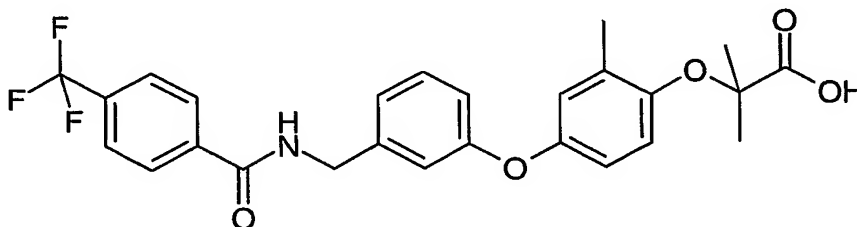


15 The title compound is prepared according to the general procedures described in Example 1 utilizing 4-trifluoromethyl-benzoic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{25}H_{23}NO_4F_3$  ( $M+H^+$ ): 458.1579; Found: 458.1574;  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

20

Example 140

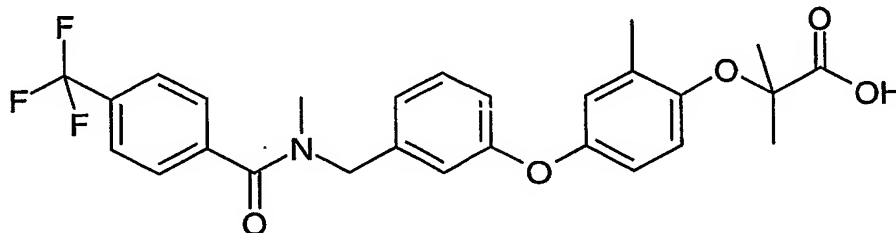
2-Methyl-2-(2-methyl-4-{3-[(4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid



- 5 The compound of 2-[4-(3-Aminomethylphenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester (Intermediate 17) (53 mg, 0.15 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.5 mL) is treated sequentially at RT with N-methyl morpholine (26 mL, 0.24 mmol) and 4-trifluoromethylbenzoyl chloride (36 mL, 0.24 mmol). After 16 h, tris(2-aminoethyl)amine resin (250 mg, 4.4 mmolN/g) is added. The mixture is stirred for 3 h, filtered, and
- 10 concentrated. The residue is diluted in THF (0.5 mL) and MeOH (1 mL) and then treated with 2N NaOH (0.5 mL). The mixture is heated at 52 °C for 2 h, cooled, and concentrated. The residue is diluted with  $\text{CH}_2\text{Cl}_2$  (1 mL) and 5 N HCl (0.8 mL) and passed through a ChemElute solid phase extraction cartridge ( $\text{CH}_2\text{Cl}_2$  eluent). The crude product was purified by mass-directed HPLC to give the title compound (41 mg, 56%):
- 15 MS: ( $\text{ES}^+$ ) 488.2 ( $\text{M}+\text{H}^+$ )

Example 141

2-Methyl-2-[2-methyl-4-(3-{[methyl-(4-trifluoromethyl-benzoyl)-amino]-methyl}-phenoxy)-phenoxy]-propionic acid



Step A

2-Methyl-2-(2-methyl-4-{3-[(4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-  
phenoxy)-propionic acid ethyl ester

The title compound is prepared according to the general procedures  
described in Example 1, Step A utilizing 4-trifluoromethyl-benzoic acid and 2-[4-(3-  
aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester  
(Intermediate 17). MS: (ES<sup>+</sup>) 516.3 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Step B

2-Methyl-2-[2-methyl-4-(3-{[methyl-(4-trifluoromethyl-benzoyl)-amino]-methyl}-  
phenoxy)-phenoxy]-propionic acid ethyl ester

To NaH (0.0090g, 0.22mmol) in dry DMF (1ml) is added the compound of  
Step A above (0.0800g, 0.16mmol) in dry DMF (1 ml) at rt. The mixture is stirred for 20  
min, cooled to 0-5°C, and then MeI (0.02 ml, 0.38mmol) in dry DMF (1 ml) is added. The  
mixture is stirred at 0-5°C for 2h, and then rt overnight. The mixture is acidified with 1M  
HCl and diluted with EtOAc, which is then washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>,  
filtered and concentrated. Purification by chromatography by eluting with 20 % EtOAc  
in hexane, and 30 % EtOAc in hexane provides the title compound (0.02g) as well as  
methyl ester side product (0.04g) and a mixture of the ethyl ester and methyl ester  
(0.01g). For the title compound: MS: (ES<sup>+</sup>) 530.3 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).  
For the methyl ester: MS: (ES<sup>+</sup>) 516.3 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

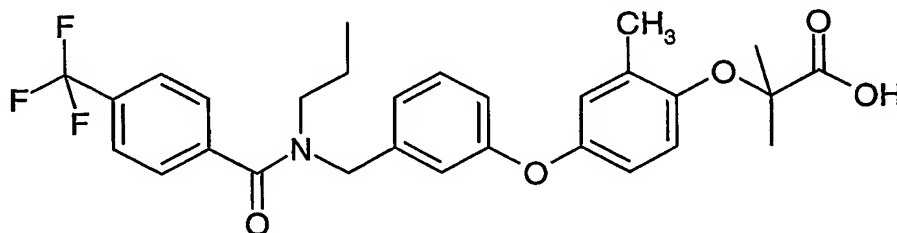
Step C

2-Methyl-2-[2-methyl-4-(3-{[methyl-(4-trifluoromethyl-benzoyl)-amino]-methyl}-  
phenoxy)-phenoxy]-propionic acid

The title compound and the methyl ester from Step B above are combined  
(0.07g) and dissolved in dioxane (4 ml). LiOH·H<sub>2</sub>O (0.10g, 2.4 mmol) in H<sub>2</sub>O (2 ml) is  
added and stirred at rt overnight. The mixture is acidified with 1M HCl and concentrated.  
MS: (ES<sup>+</sup>) 502.3 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

Example 142

2-Methyl-2-[2-methyl-4-(3-[[propyl-(4-trifluoromethyl-benzoyl)-amino]-methyl]-phenoxy)-phenoxy]-propionic acid

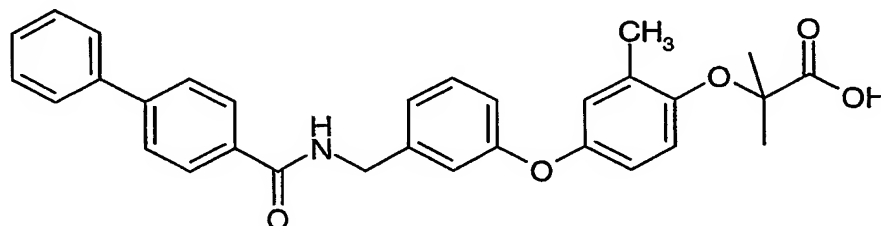


5 The title compound is prepared according to Example 141 utilizing 2-methyl-2-(2-methyl-4-{3-[(4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid ethyl ester (Example 141, Step A) and 1-iodo-propane. MS: (ES<sup>+</sup>) 530.4 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

10

Example 143

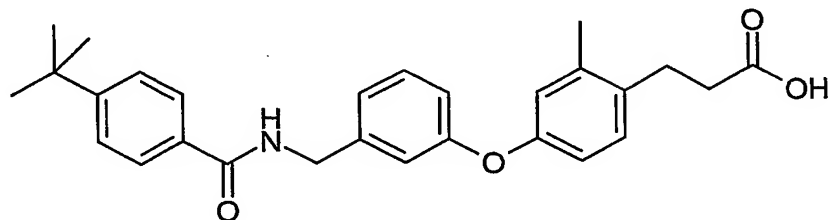
2-[4-(3-[[[Biphenyl-4-carbonyl)-amino]-methyl]-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid



15 The title compound is prepared according to the general procedures described in Example 1 utilizing biphenyl-4-carboxylic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid (Intermediate 17). Exact mass calcd for C<sub>31</sub>H<sub>30</sub>NO<sub>5</sub> (M+H<sup>+</sup>): 496.2124, found 496.2114; <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>).

Example 144

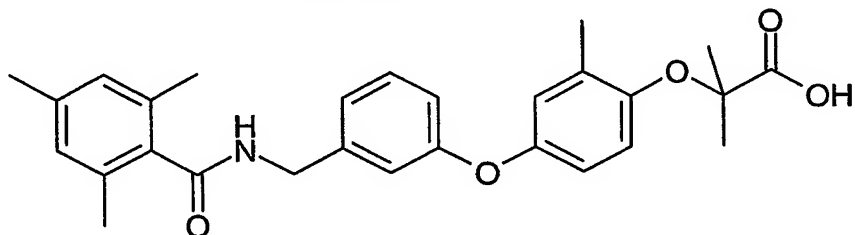
3-(4-{3-[(4-tert-Butyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenyl)-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 4-tert-butyl-benzoic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{28}H_{32}NO_4$  ( $M+H^+$ ): 446.2331, found 446.2358;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 145

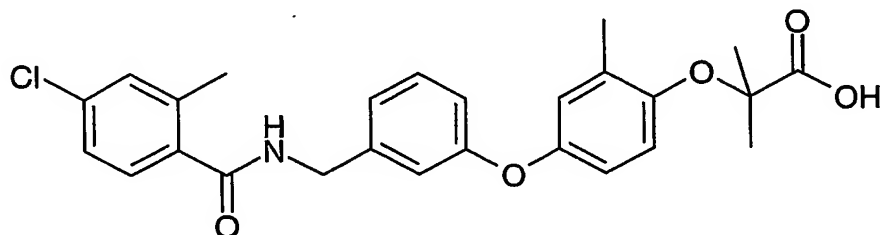
2-Methyl-2-(2-methyl-4-{3-[(2,4,6-trimethyl-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 2,4,6-trimethyl-benzoic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{28}H_{32}NO_5$  ( $M+H^+$ ): 462.2280, found 462.2295;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 146

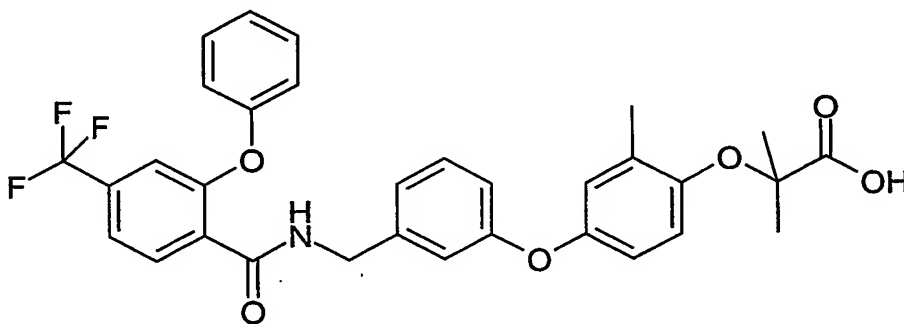
2-(4-{3-[(4-Chloro-2-methyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 4-chloro-2-methyl-benzoic acid and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{26}H_{27}NO_5Cl$  ( $M+H^+$ ): 468.1578, found 468.1585;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 147

2-Methyl-2-(2-methyl-4-{3-[(2-phenoxy-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenoxy)-propionic acid

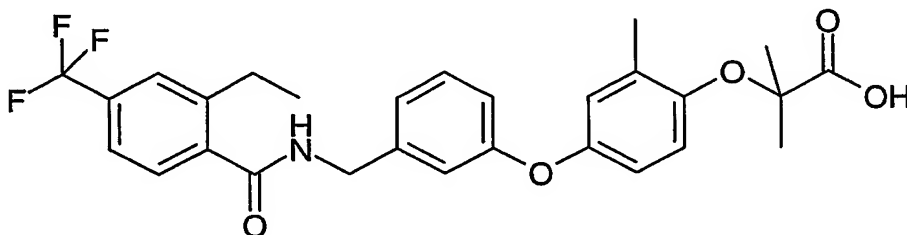


The title compound is prepared according to the general procedures described in Example 1 utilizing 2-phenoxy-4-trifluoromethyl-benzoic acid (Intermediate 31) and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{32}H_{29}NO_6F_3$  ( $M+H^+$ ): 580.1947, found 580.1931;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).



Example 148

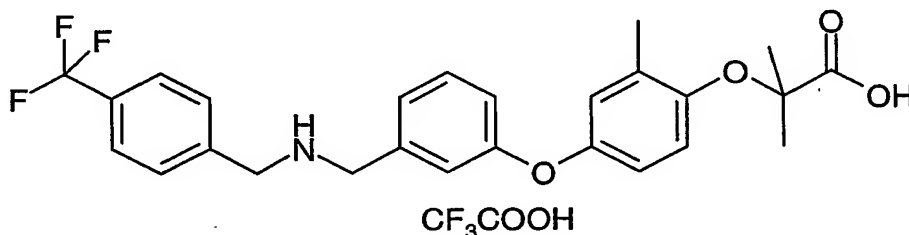
2-(4-{3-[(2-Ethyl-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 2-ethyl-4-trifluoromethyl-benzoic acid (Intermediate 30) and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{28}H_{29}NO_5F_3$  ( $M+H^+$ ): 516.1998, found 516.2004;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 149

2-Methyl-2-(2-methyl-4-{3-[(4-trifluoromethyl-benzylamino)-methyl]-phenoxy}-phenoxy)-propionic acid; compound with trifluoro-acetic acid

Step A

2-Methyl-2-(2-methyl-4-{3-[(4-trifluoromethyl-benzylamino)-methyl]-phenoxy}-phenoxy)-propionic acid ethyl ester

The compound of 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17) (0.34 g, 0.99 mmol) is dissolved in MeOH (10 ml), and NaOAc (0.32g, 4.0 mmol) is added. The mixture is stirred at 0 °C. The compound of 4-(trifluoromethyl)benzaldehyde (0.12 ml, 0.89 mmol) is added and then stirred at 0 °C for 15 min.  $NaBH_3CN$  (0.09 g, 1.5 mmol) is added followed by a few drops of HOAc. The mixture is stirred at 0 °C for 1.5h and then concentrated. The

residue is partitioned in EtOAc and water. The EtOAc layer is separated, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. Purification by chromatography, eluting with 2% MeOH in CH<sub>2</sub>Cl<sub>2</sub> provides the title compound (0.35g). MS: (ES<sup>+</sup>) 502.3 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

5

### Step B

2-Methyl-2-(2-methyl-4-{3-[(4-trifluoromethyl-benzylamino)-methyl]-phenoxy}-phenoxy)-propionic acid; compound with trifluoro-acetic acid

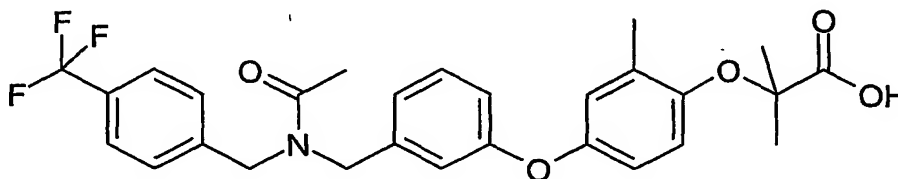
The title compound is prepared according to the general procedures described in Example 1, Step B utilizing the compound from Step A above and purified by reversed HPLC. Exact mass calcd for C<sub>26</sub>H<sub>27</sub>NO<sub>4</sub>F<sub>3</sub> (M+H<sup>+</sup>): 474.1892, found 474.1877; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

10

### Example 150

2-[4-(3-{[Acetyl-(4-trifluoromethyl-benzyl)-amino]-methyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid

15



### Step A

2-[4-(3-{[Acetyl-(4-trifluoromethyl-benzyl)-amino]-methyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester

20

The compound of 2-methyl-2-(2-methyl-4-{3-[(4-trifluoromethyl-benzylamino)-methyl]-phenoxy}-phenoxy)-propionic acid ethyl ester (Example 149, Step A, 0.10 g, 0.20 mmol) is mixed with (CH<sub>3</sub>CO)<sub>2</sub>O (1.5 ml) and stirred at rt for 1.5h. The mixture is concentrated at 35 °C under vacuum. The residue is dissolved in EtOAc, washed with 1M HCl, diluted NaHCO<sub>3</sub> and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. Purification by chromatography by eluting with 15% EtOAc in hexane and 25 % EtOAc in hexane provides the title compound (0.08g). MS: (ES<sup>+</sup>) 544.3 (M+H<sup>+</sup>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

25

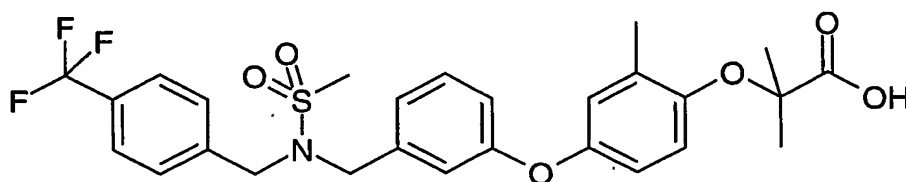
Step B

2-[4-(3-{[Acetyl-(4-trifluoromethyl-benzyl)-amino]-methyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid

The title compound is prepared according to the general procedures described in Example 1, Step B, utilizing the compound of Step A above. Exact mass calcd for  $C_{28}H_{29}NO_5F_3$  ( $M+H^+$ ): 516.1998, found 516.2004;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 151

2-[4-(3-{[Methanesulfonyl-(4-trifluoromethyl-benzyl)-amino]-methyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid

Step A

2-[4-(3-{[Methanesulfonyl-(4-trifluoromethyl-benzyl)-amino]-methyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester

The compound of 2-methyl-2-(2-methyl-4-{3-[(4-trifluoromethyl-benzylamino)-methyl]-phenoxy}-phenoxy)-propionic acid ethyl ester (Example 149, Step A, 0.13 g, 0.26 mmol) is dissolved in  $CH_2Cl_2$  (5 ml), and  $Et_3N$  (0.05 ml, 0.39 mmol) is added. The mixture is cooled to 0 °C, and  $MsCl$  (0.04 ml, 0.31 mmol) is added, which is then stirred at 0 °C to rt for 4h. The mixture is diluted with  $CH_2Cl_2$ , washed with 1M  $HCl$ , diluted  $NaHCO_3$  and brine, dried over  $Na_2SO_4$ , filtered and concentrated. Purification by chromatography, eluting with 15%  $EtOAc$  in hexane, then 25 %  $EtOAc$  in hexane provides the title compound (0.11g). MS: ( $ES^+$ ) 597.2 ( $M+NH_4^+$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ ).

Step B

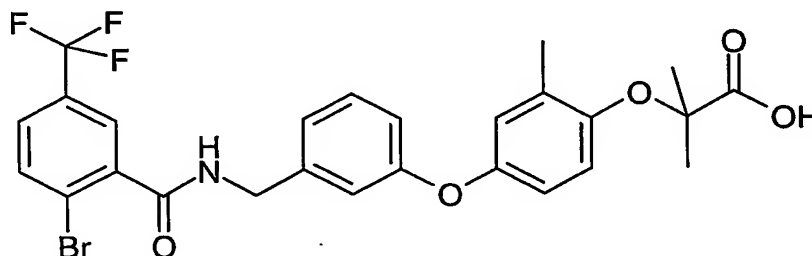
(2-[4-(3-{[Methanesulfonyl-(4-trifluoromethyl-benzyl)-amino]-methyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid

The title compound is prepared according to the general procedures described in Example 1, Step B utilizing the compound of Step A above. Exact mass

calcd for  $C_{27}H_{32}N_2O_6F_3$  ( $M+NH_4^+$ ): 569.1933, found 569.1926;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

### Example 152

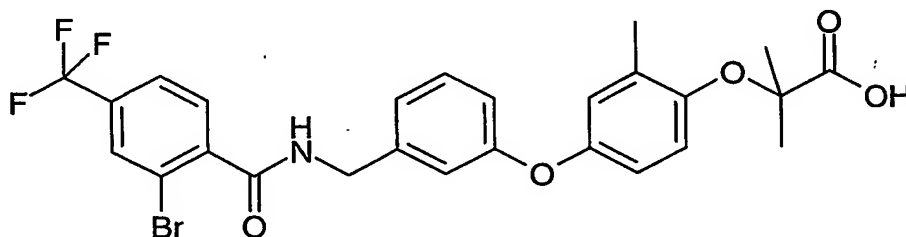
- 5      2-(4-{3-[(2-Bromo-5-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



- The title compound is prepared according to the general procedures described in Example 1 utilizing 2-bromo-5-trifluoromethyl-benzoic acid (*Tetrahedron Lett.*, Vol.37, No.16, pp. 2767-2770, 1996) and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{26}H_{24}NO_5F_3Br$  ( $M+H^+$ ): 566.0790, found 566.0787;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

### Example 153

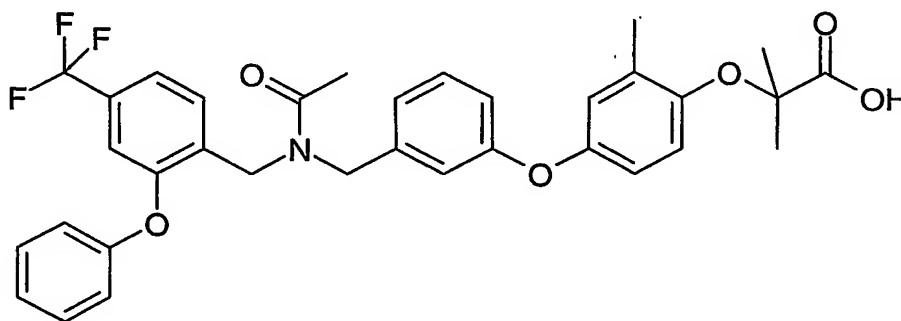
- 15      2-(4-{3-[(2-Bromo-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



- The title compound is prepared according to the general procedures described in Example 1 utilizing 2-bromo-4-trifluoromethyl-benzoic acid (Intermediate 11) and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). The final product is purified by reversed HPLC. MS: ( $ES^+$ ) 566 / 568 ( $M+H^+$ ).

Example 154

2-[4-(3-{[Acetyl-(2-phenoxy-4-trifluoromethyl-benzyl)-amino]-methyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid

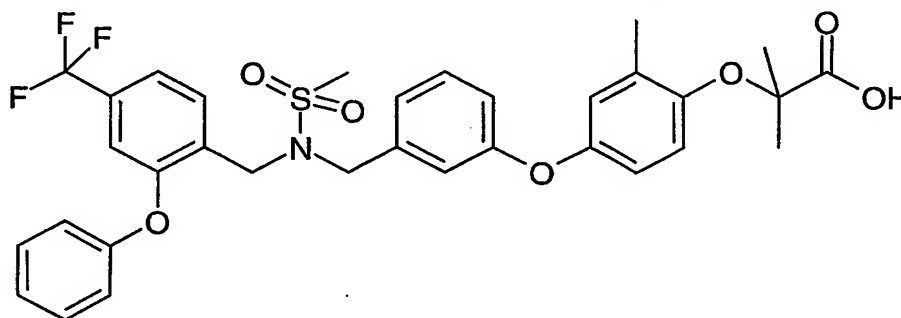


5 The title compound is prepared according to Example 150 utilizing 2-Phenoxy-4-trifluoromethyl-benzaldehyde (Intermediate 32) and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{34}H_{33}NO_6F_3$  ( $M+H^+$ ): 608.2260, found 608.2253;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

10

Example 155

2-[4-(3-{[Methanesulfonyl-(2-phenoxy-4-trifluoromethyl-benzyl)-amino]-methyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid

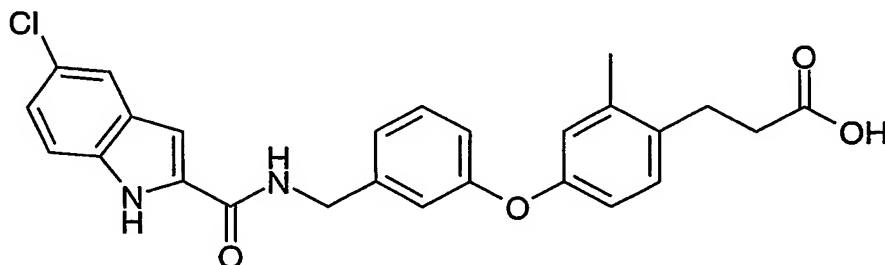


15 The title compound is prepared according to Example 151 utilizing 2-phenoxy-4-trifluoromethyl-benzaldehyde (Intermediate 32) and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{33}H_{36}N_2O_7F_3S$  ( $M+NH_4^+$ ): 661.2195, found 661.2197;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

20

Example 156

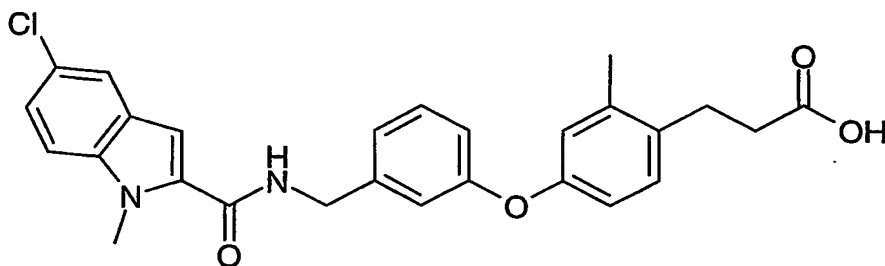
3-[4-(3-[[5-Chloro-1H-indole-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-1H-indole-2-carboxylic acid and 3-[4-(3-Aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{26}H_{24}N_2O_4Cl$  ( $M+H^+$ ): 463.1425, found 463.1402;  $^1H$ NMR (400 MHz, DMSO- $D_6$ ).

Example 157

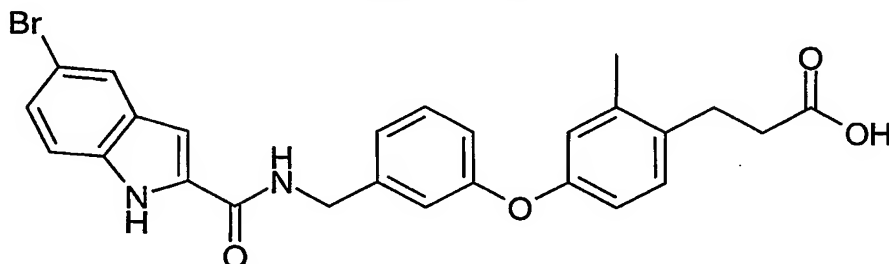
3-[4-(3-[[5-Chloro-1-methyl-1H-indole-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-1-methyl-1H-indole-2-carboxylic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{27}H_{26}N_2O_4Cl$  ( $M+H^+$ ): 477.1581, found 477.1598;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 158

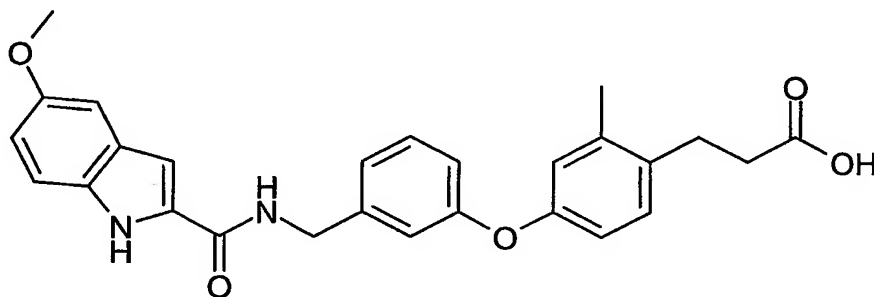
3-[4-(3-[[5-Bromo-1H-indole-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-bromo-1H-indole-2-carboxylic acid and 3-[4-(3-Aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{26}H_{24}N_2O_4Br$  ( $M+H^+$ ): 507.0919, found 507.0909;  $^1H$ NMR (400 MHz, DMSO- $D_6$ ).

Example 159

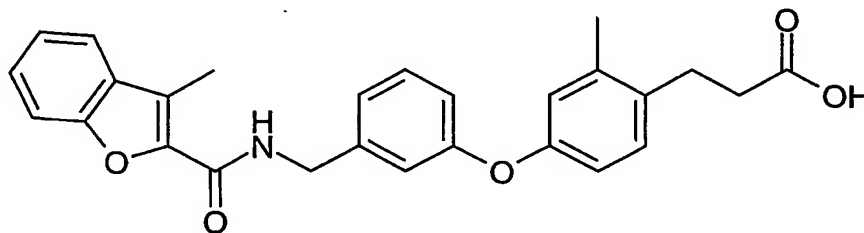
3-[4-(3-[[5-Methoxy-1H-indole-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-methoxy-1H-indole-2-carboxylic acid and 3-[4-(3-Aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{27}H_{27}N_2O_5$  ( $M+H^+$ ): 459.1920, found 459.1918;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 160

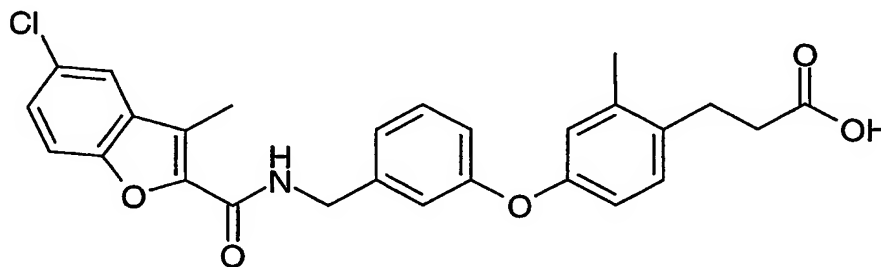
3-[2-Methyl-4-(3-[[3-methyl-benzofuran-2-carbonyl]-amino]-methyl)-phenoxy]-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 3-methyl-benzofuran-2-carboxylic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{27}H_{26}NO_5$  ( $M+H^+$ ): 444.1811, found 444.1791;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 161

3-[4-(3-[[5-Chloro-3-methyl-benzofuran-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid

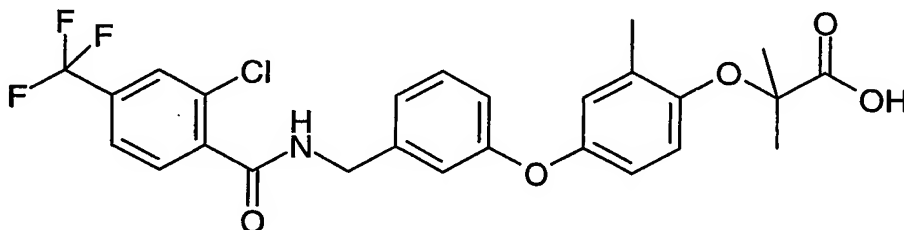


The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-3-methyl-benzofuran-2-carboxylic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{27}H_{25}NO_5Cl$  ( $M+H^+$ ): 478.1421, found 478.1398;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).



Example 162

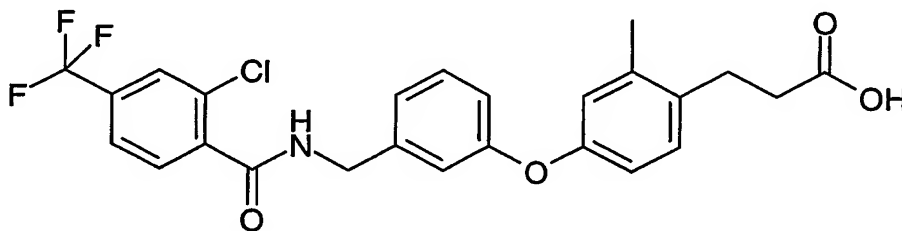
2-(4-{3-[(2-Chloro-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 2-chloro-4-trifluoromethyl-benzoic acid (Intermediate 12) and 2-[4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 17). Exact mass calcd for  $C_{26}H_{24}NO_5F_3Cl$  ( $M+H^+$ ): 522.1295, found 522.1310;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 163

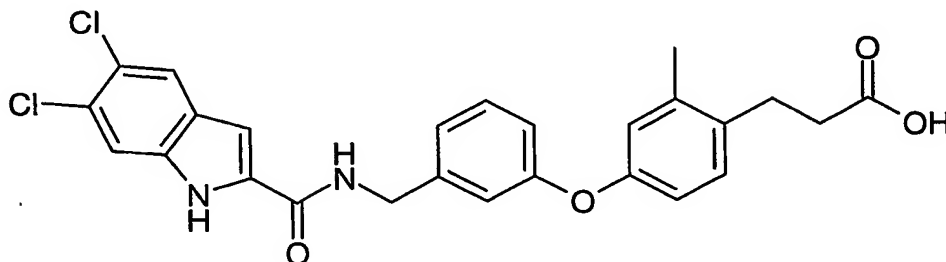
3-(4-{3-[(2-Chloro-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenyl)-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 2-chloro-4-trifluoromethyl-benzoic acid (Intermediate 12) and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{25}H_{22}NO_4F_3Cl$  ( $M+H^+$ ): 492.1189, found 492.1202;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 164

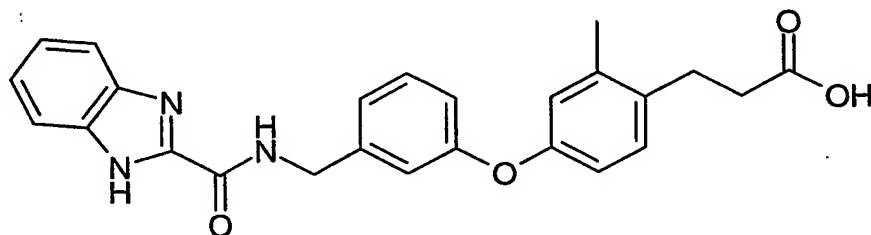
3-[4-(3-[[5,6-Dichloro-1H-indole-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5,6-dichloro-1H-indole-2-carboxylic acid (WO 9935130) and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{26}H_{23}N_2O_4Cl_2$  ( $M+H^+$ ): 497.1035, found 497.1043;  $^1H$ NMR (400 MHz,  $CD_3OD$ ).

Example 165

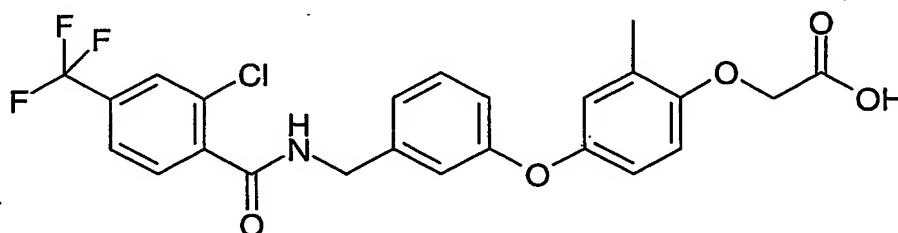
3-[4-(3-[[1H-Benzoimidazole-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 1H-benzimidazole-2-carboxylic acid and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33). Exact mass calcd for  $C_{25}H_{24}N_3O_4$  ( $M+H^+$ ): 430.1767, found 430.1772;  $^1H$ NMR (400 MHz,  $DMSO-D_6$ ).

Example 166

(2-Methyl-4-{3-[(2-methyl-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-  
phenoxy)-acetic acid

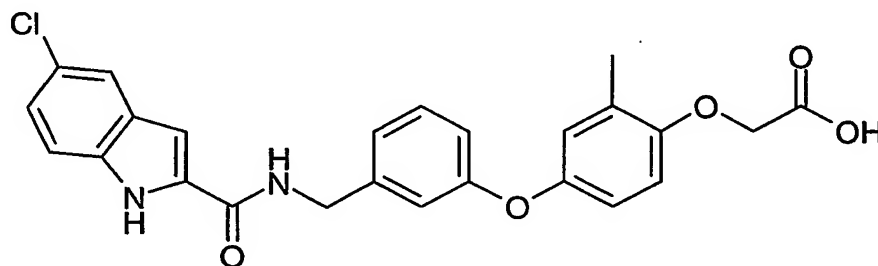


5           The title compound is prepared according to the general procedures described in Example 1 utilizing 2-chloro-4-trifluoromethyl-benzoic acid (Intermediate 12) and [4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-acetic acid methyl ester (Intermediate 35). Exact mass calcd for  $C_{25}H_{23}NO_5F_3$  ( $M+H^+$ ): 474.1528, found 474.1549;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

10

Example 167

[4-(3-[[5-Chloro-1H-indole-2-carbonyl]-amino]-methyl)-phenoxy]-2-methyl-phenoxy]-  
acetic acid

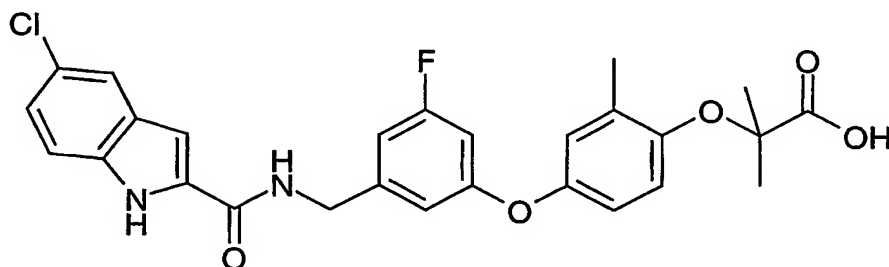


15           The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-1H-indole-2-carboxylic acid and [4-(3-aminomethyl-phenoxy)-2-methyl-phenoxy]-acetic acid methyl ester (Intermediate 35). MS: ( $ES^+$ ) 465.1 ( $M+H^+$ );  $^1H$  NMR (400 MHz, DMSO- $D_6$ ).

20

Example 168

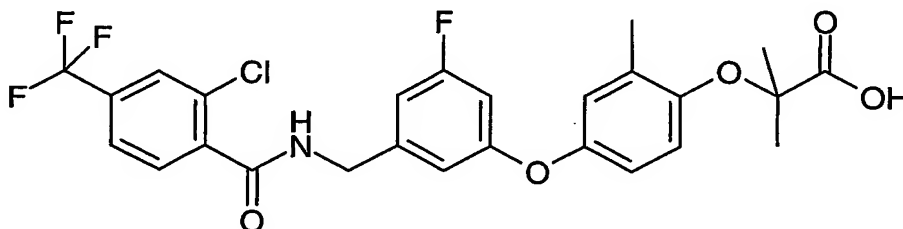
2-[4-(3-[[5-Chloro-1H-indole-2-carbonyl]-amino]-methyl)-5-fluoro-phenoxy]-2-methyl-phenoxy]-2-methyl-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-1H-indole-2-carboxylic acid and 2-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 47). Exact mass calcd for  $C_{27}H_{25}N_2O_5FCl$  ( $M+H^+$ ): 511.1436, found 511.1447;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 169

2-(4-{3-[(2-Chloro-4-trifluoromethyl-benzoylamino)-methyl]-5-fluoro-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid

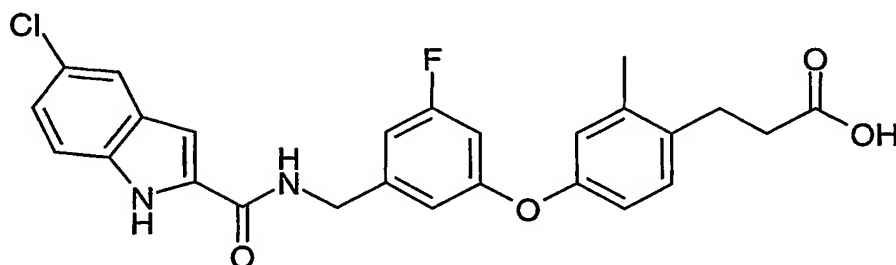


The title compound is prepared according to the general procedures described in Example 1 utilizing 2-chloro-4-trifluoromethyl-benzoic acid (Intermediate 12) and 2-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 47). Exact mass calcd for  $C_{26}H_{23}NO_5F_4Cl$  ( $M+H^+$ ): 540.1201, found 540.1218;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).



Example 172

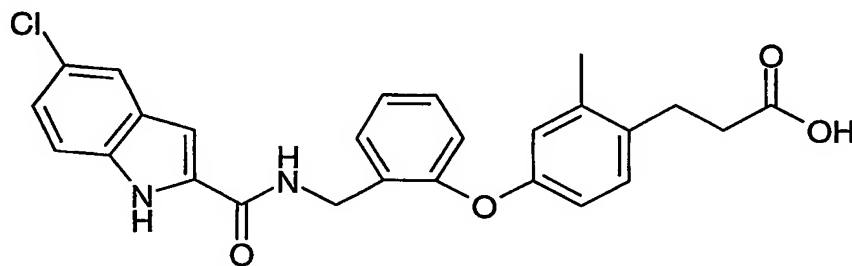
3-[4-(3-[[5-Chloro-1H-indole-2-carbonyl]-amino]-methyl)-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-1H-indole-2-carboxylic acid and [4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenoxy]-acetic acid methyl ester (Intermediate 36). Exact mass calcd for  $C_{26}H_{23}N_2O_4FCl$  ( $M+H^+$ ): 481.1330, found 481.1357;  $^1H$ NMR (400 MHz, DMSO- $D_6$ ).

Example 173

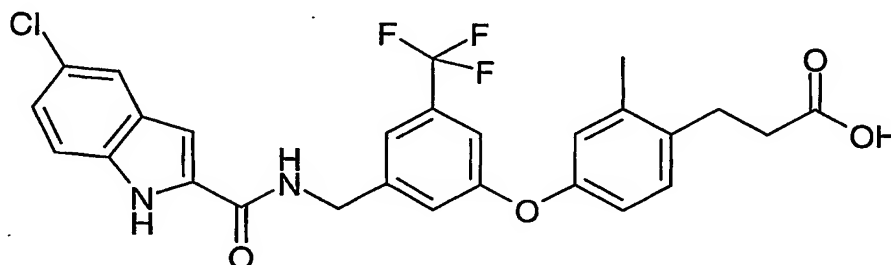
3-[4-(2-[[5-Chloro-1H-indole-2-carbonyl]-amino]-methyl)-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-1H-indole-2-carboxylic acid and 3-[4-(2-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 37). Exact mass calcd for  $C_{26}H_{24}N_2O_4Cl$  ( $M+H^+$ ): 463.1424, found 463.1437;  $^1H$ NMR (400 MHz, DMSO- $D_6$ ).

Example 174

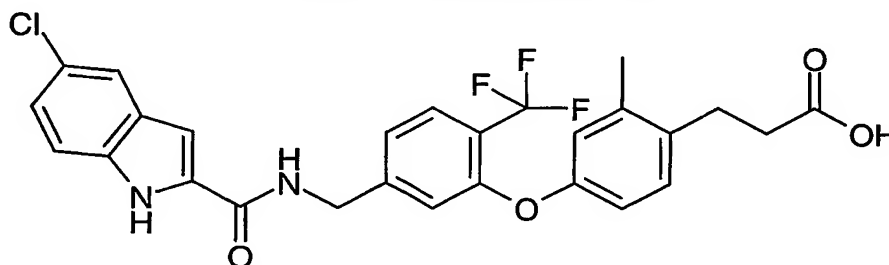
3-[4-(3-[[5-Chloro-1H-indole-2-carbonyl]-amino]-methyl)-5-trifluoromethyl-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-1H-indole-2-carboxylic acid and 3-[4-(3-aminomethyl-5-trifluoromethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 38). Exact mass calcd for  $C_{27}H_{23}N_2O_4ClF_3$  ( $M+H^+$ ): 531.1298, found 531.1312;  $^1H$ NMR (400 MHz, DMSO- $D_6$ ).

Example 175

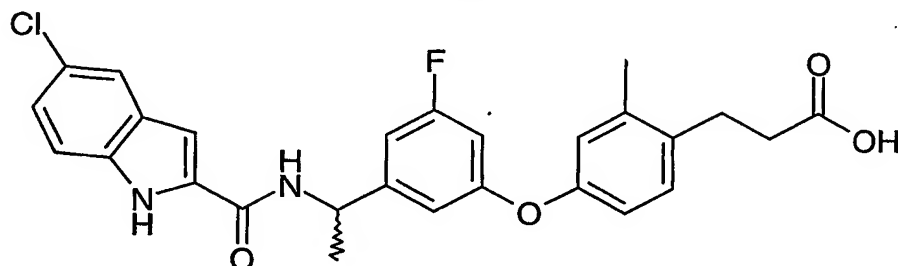
3-[4-(5-[[5-Chloro-1H-indole-2-carbonyl]-amino]-methyl)-2-trifluoromethyl-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-1H-indole-2-carboxylic acid and 3-[4-(5-aminomethyl-2-trifluoromethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 39). Exact mass calcd for  $C_{27}H_{23}N_2O_4ClF_3$  ( $M+H^+$ ): 531.1298, found 531.1285;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 176

3-[4-(3-{1-[(5-Chloro-1H-indole-2-carbonyl)-amino]-ethyl}-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid

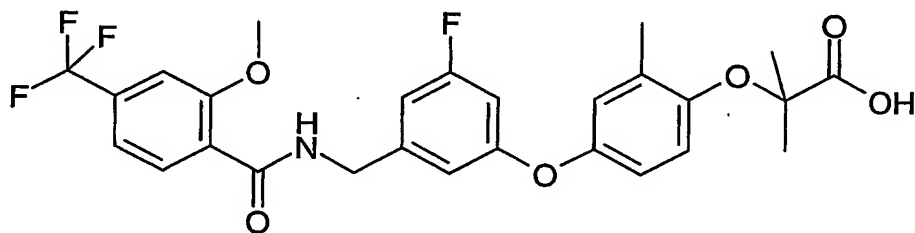


The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-1H-indole-2-carboxylic acid and 3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (Intermediate 34). Exact mass calcd for  $C_{26}H_{24}N_2O_4Cl$  ( $M+H^+$ ): 495.1487, found 495.1471;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

The pure enantiomers are separated by chiral chromatography at the ester stage and hydrolyzed separately to provide isomer 1 (R configuration) and isomer 2 (S configuration). Isomer 1: Exact mass calcd for  $C_{26}H_{24}N_2O_4Cl$  ( $M+H^+$ ): 495.1487, found 495.1466;  $^1H$ NMR (400 MHz,  $CDCl_3$ ). Isomer 2: Exact mass calcd for  $C_{26}H_{24}N_2O_4Cl$  ( $M+H^+$ ): 495.1487, found 495.1465;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 177

2-(4-{3-Fluoro-5-[(2-methoxy-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



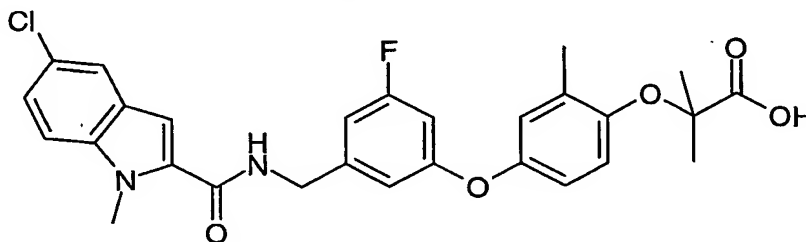
The title compound is prepared according to the general procedures described in Example 1 utilizing 2-methoxy-4-trifluoromethyl-benzoic acid (*J.Am.Chem.Soc.*; 73; 1951; 2375) and 2-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-



methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 47). Exact mass calcd for  $C_{27}H_{26}NO_6F_4$  ( $M+H^+$ ): 536.1696, found 536.1706;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

#### Example 178

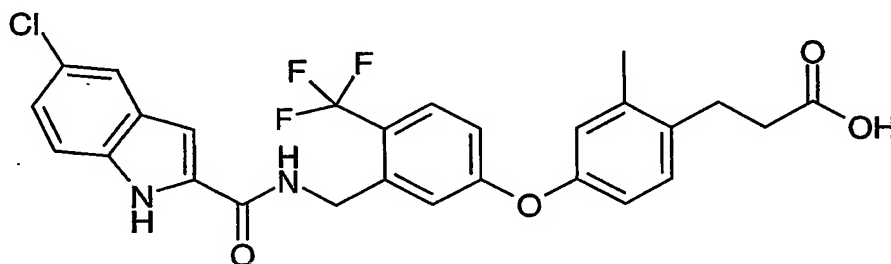
- 5 2-[4-(3-[[[(5-Chloro-1-methyl-1H-indole-2-carbonyl)-amino]-methyl]-5-fluoro-phenoxy]-2-methyl-phenoxy]-2-methyl-propionic acid



- The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-1-methyl-1H-indole-2-carboxylic acid and 2-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 47). Exact mass calcd for  $C_{28}H_{27}N_2O_5FCl$  ( $M+H^+$ ): 525.1592, found 525.1592;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

#### Example 179

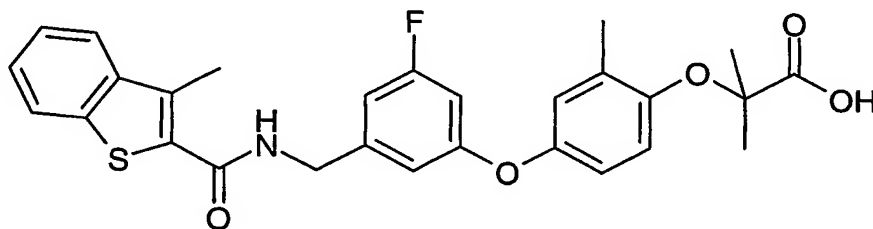
- 15 3-[4-(3-[[[(5-Chloro-1H-indole-2-carbonyl)-amino]-methyl]-4-trifluoromethyl-phenoxy]-2-methyl-phenyl]-propionic acid



- The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-1H-indole-2-carboxylic acid and 3-[4-(3-aminomethyl-4-trifluoromethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 40). Exact mass calcd for  $C_{27}H_{23}N_2O_4ClF_3$  ( $M+H^+$ ): 531.1298, found 531.1307;  $^1H$ NMR (400 MHz,  $DMSO-D_6$ ).

Example 180

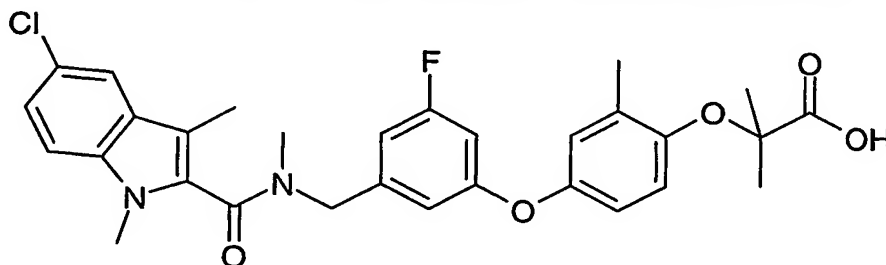
2-[4-(3-Fluoro-5-[[[(3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-methyl]-phenoxy]-2-methyl-phenoxy]-2-methyl-propionic acid



5 The title compound is prepared according to the general procedures described in Example 1 utilizing 3-methyl-benzo[b]thiophene-2-carboxylic acid and 2-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 47). Exact mass calcd for  $C_{28}H_{27}NO_5FS$  ( $M+H^+$ ): 508.1594, found 508.1588;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 181

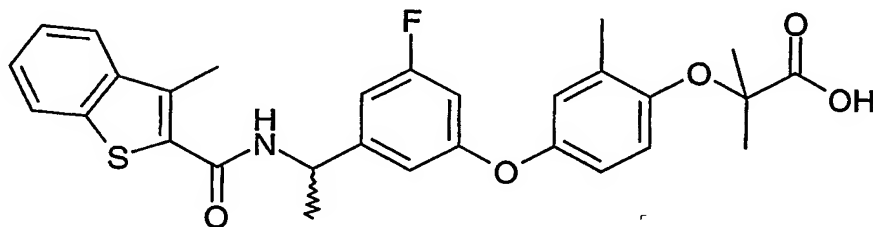
2-[4-(3-[[[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-methyl-amino]-methyl]-5-fluoro-phenoxy]-2-methyl-phenoxy]-2-methyl-propionic acid



15 The title compound is prepared according to the procedure described in Example 141 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and 2-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 47). Exact mass calcd for  $C_{30}H_{29}N_2O_5FCl$  ( $M-H^+$ ): 551.1749, found 551.1747;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 182

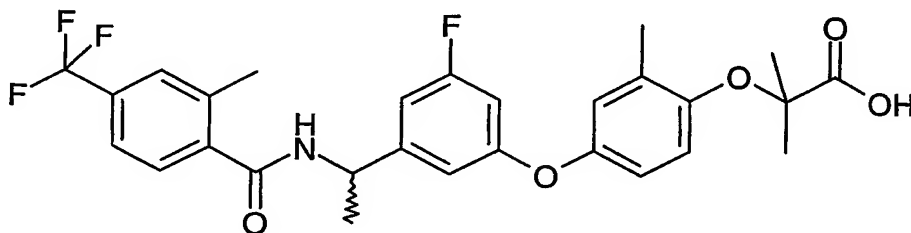
2-[4-(3-Fluoro-5-{1-[(3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 3-methyl-benzo[b]thiophene-2-carboxylic acid and 2-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl ester (Intermediate 41). Exact mass calcd for  $C_{29}H_{29}NO_5FS$  ( $M+H^+$ ): 522.1750, found 522.1741;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 183

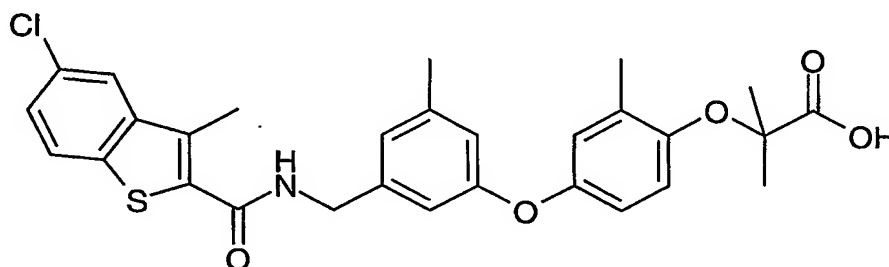
2-(4-{3-Fluoro-5-[1-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 2-methyl-4-trifluoromethyl-benzoic acid (Intermediate 10) and 2-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl ester (Intermediate 41). Exact mass calcd for  $C_{28}H_{28}NO_5F_4$  ( $M+H^+$ ): 534.1904, found 534.1885;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 184

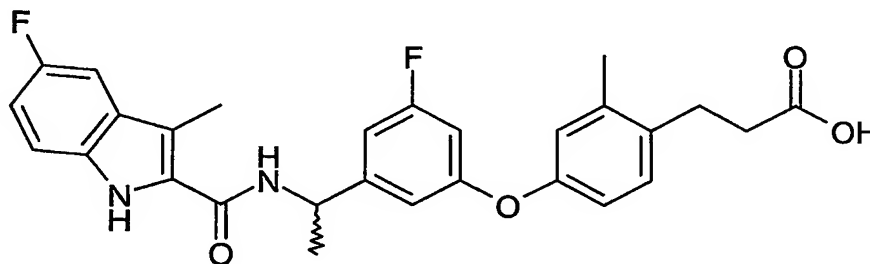
2-[4-(3-[(5-Chloro-3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-methyl)-5-methyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-3-methyl-benzo[b]thiophene-2-carboxylic acid and 2-[4-(3-aminomethyl-5-methyl-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 20). Exact mass calcd for  $C_{29}H_{29}ClNO_5S$  ( $M+H^+$ ): 538.1455, found 538.1454;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 185

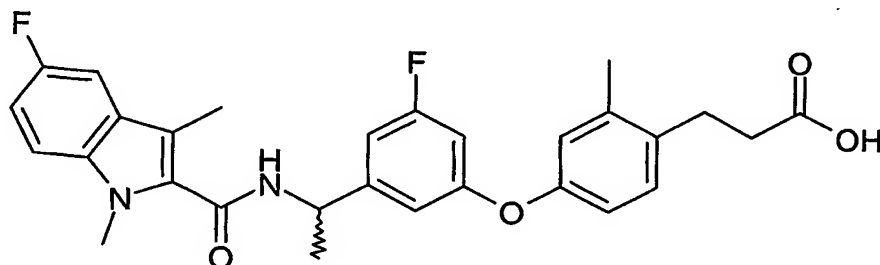
3-[4-(3-Fluoro-5-{1-[(5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-fluoro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 1) and 3-[4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 34). Exact mass calcd for  $C_{28}H_{26}F_2N_2O_4$  ( $M+H^+$ ): 493.1939, found 493.1950;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 186

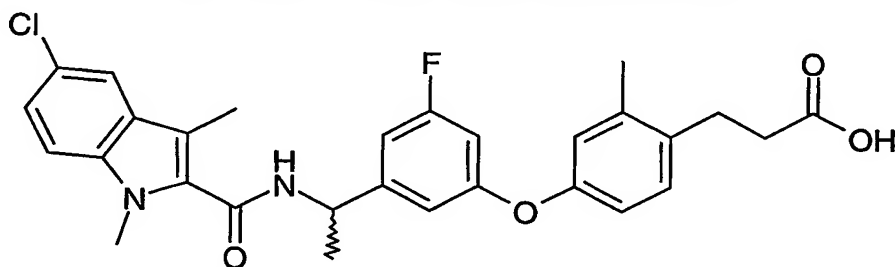
3-[4-(3-Fluoro-5-{1-[(5-fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 2) and 3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (Intermediate 34). Exact mass calcd for  $C_{29}H_{29}F_2N_2O_4$  ( $M+H^+$ ): 507.2095, found 507.2097;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 187

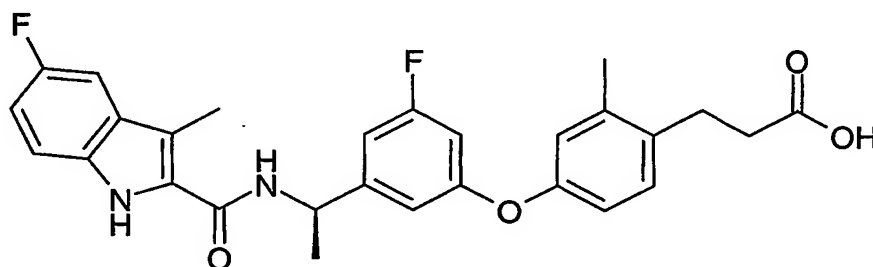
3-[4-(3-{1-[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and 3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (Intermediate 34). Exact mass calcd for  $C_{29}H_{29}ClFN_2O_4$  ( $M+H^+$ ): 523.1800, found 523.1782;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 188

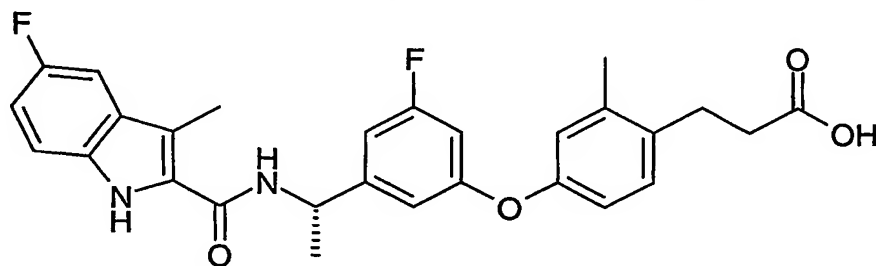
( R ) -3-[4-(3-Fluoro-5-{ 1-[(5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the procedure described in Example 176 from 3-[4-(3-{ 1-[(5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Example 185). Exact mass calcd for  $C_{28}H_{27}F_2N_2O_4$  ( $M+H^+$ ): 493.1939, found 493.1946;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 189

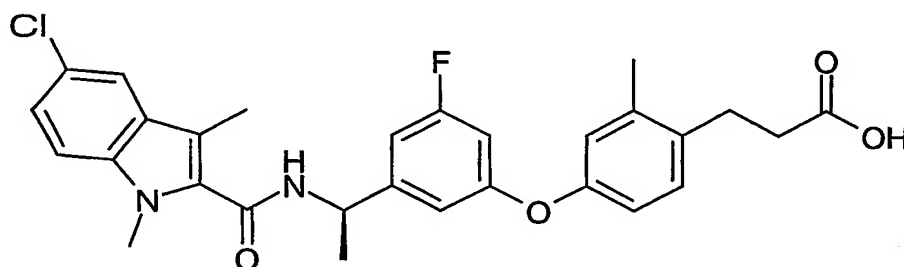
( S ) -3-[4-(3-Fluoro-5-{ 1-[(5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-ethyl}-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the procedure described in Example 176 from 3-[4-(3-{ 1-[(5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Example 185). Exact mass calcd for  $C_{28}H_{27}F_2N_2O_4$  ( $M+H^+$ ): 493.1939, found 493.1930;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 190

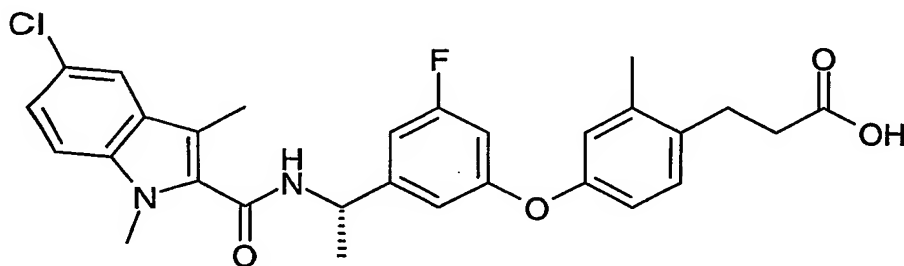
( R )-3-[4-(3-{ 1-[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the procedure described in Example 176 from 3-[4-(3-{ 1-[(5-chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Example 187). Exact mass calcd for  $C_{29}H_{29}ClFN_2O_4$  ( $M+H^+$ ): 523.1800, found 523.1789;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 191

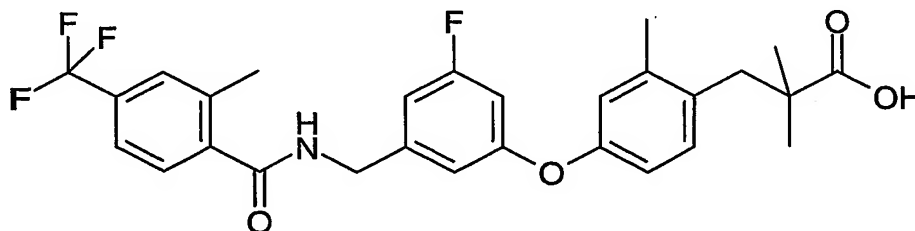
( S )-3-[4-(3-{ 1-[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the procedure described in Example 176 from 3-[4-(3-{ 1-[(5-chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Example 187). Exact mass calcd for  $C_{29}H_{29}ClFN_2O_4$  ( $M+H^+$ ): 523.1800, found 523.1794;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 192

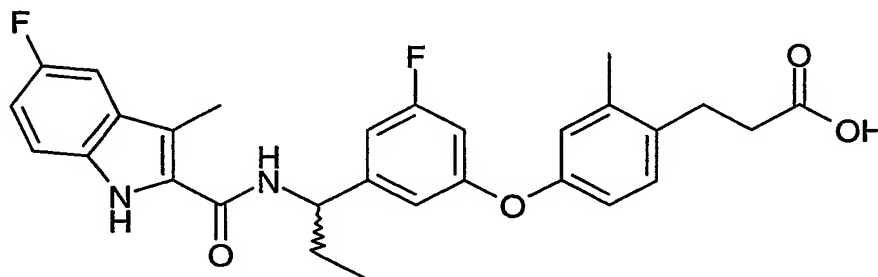
3-(4-{3-Fluoro-5-[(2-methyl-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenyl)-2,2-dimethyl-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 2-methyl-4-trifluoromethyl-benzoic acid (Intermediate 10) and 3-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenyl]-2,2-dimethyl-propionic acid methyl ester (Intermediate 42). Exact mass calcd for  $C_{28}H_{28}NO_4F_4$  ( $M+H^+$ ): 518.1954, found 518.1943;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 193

3-[4-(3-Fluoro-5-{1-[(5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-propyl}-phenoxy)-2-methyl-phenyl]-propionic acid

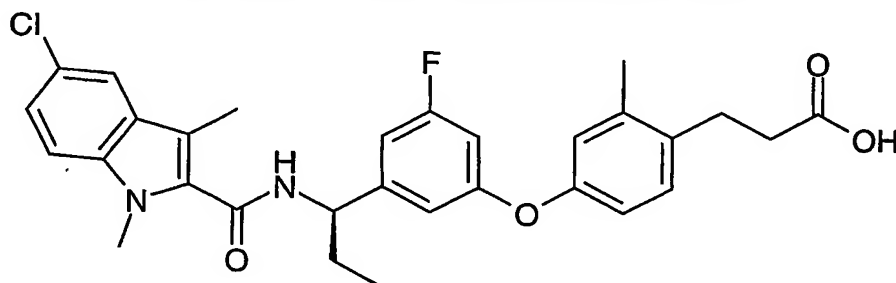


The title compound is prepared according to the general procedures described in Example 1 utilizing 5-fluoro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 1) and 3-[4-[3-(1-amino-propyl)-5-fluoro-phenoxy]-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 43). Exact mass calcd for  $C_{29}H_{29}F_2N_2O_4$  ( $M+H^+$ ): 507.2095, found 507.2085;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).



Example 194

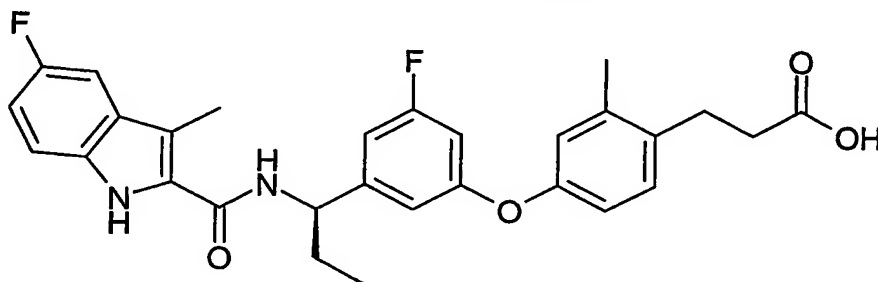
3-[4-(3-{1-[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-propyl}-5-fluoro-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and 3-{4-[3-(1-amino-propyl)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (Intermediate 44). Exact mass calcd for  $C_{30}H_{31}ClFN_2O_4$  ( $M+H^+$ ): 537.1956, found 537.1942;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 195

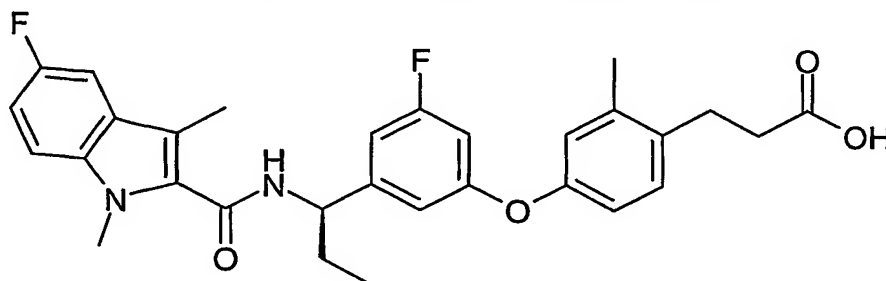
3-[4-(3-Fluoro-5-{1-[(5-fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-propyl}-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-fluoro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 1) and 3-{4-[3-(1-amino-propyl)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (Intermediate 44). Exact mass calcd for  $C_{29}H_{29}F_2N_2O_4$  ( $M+H^+$ ): 507.2095, found 507.2083;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 196

3-[4-(3-Fluoro-5-{1-[(5-fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-propyl}-phenoxy)-2-methyl-phenyl]-propionic acid

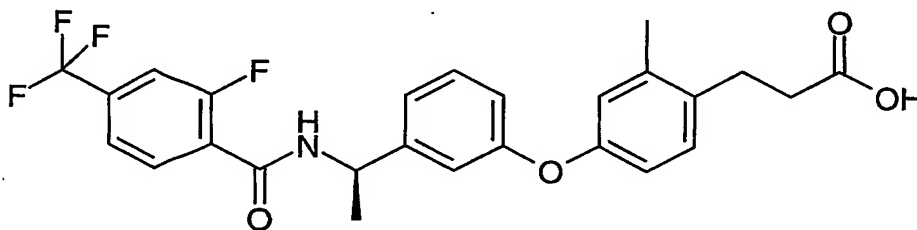


5           The title compound is prepared according to the general procedures described in Example 1 utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 2) and 3-{4-[3-(1-amino-propyl)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (Intermediate 44). Exact mass calcd for  $C_{30}H_{31}F_2N_2O_4$  ( $M+H^+$ ): 521.2252, found 521.2243;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

10

Example 197

3-(4-{3-[1-(2-Fluoro-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid

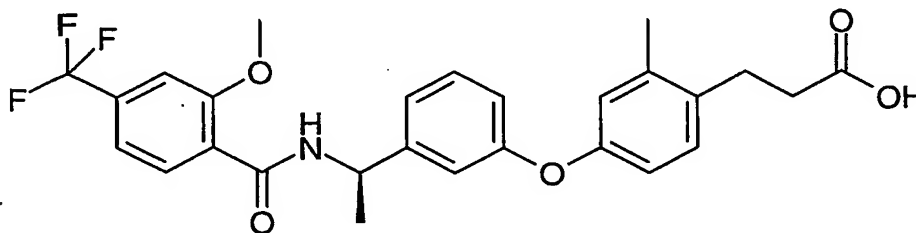


15           The title compound is prepared according to the general procedures described in Example 1 utilizing 2-fluoro-4-trifluoromethyl-benzoic acid and 3-{4-[3-(1-amino-ethyl)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (Intermediate 24). Exact mass calcd for  $C_{26}H_{23}NO_4F_4$  ( $M+H^+$ ): 490.1641, found 490.1625;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

20

Example 198

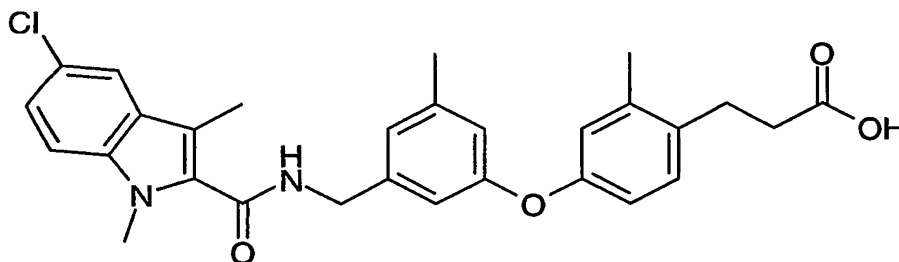
3-(4-{3-[1-(2-Methoxy-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 2-methoxy-4-trifluoromethyl-benzoic acid (*J.Am.Chem.Soc.*; 73; 1951; 2375) and 3-[4-[3-(1-amino-ethyl)-phenoxy]-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 24). Exact mass calcd for  $C_{27}H_{27}NO_5F_3$  ( $M+H^+$ ): 502.1841, found 502.1827;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 199

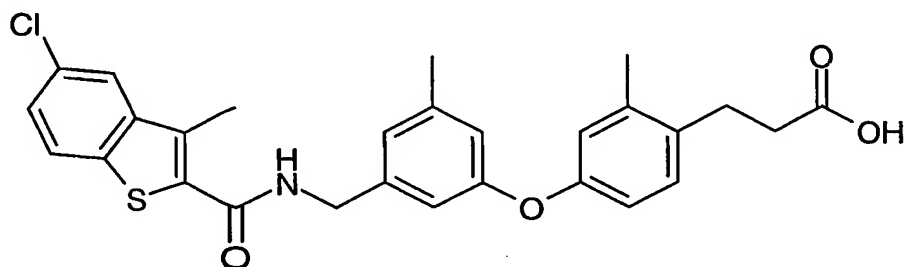
3-[4-(3-{[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl}-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and 3-[4-(3-aminomethyl-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 45). Exact mass calcd for  $C_{29}H_{30}ClN_2O_4$  ( $M+H^+$ ): 505.1894, found 505.1882;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 200

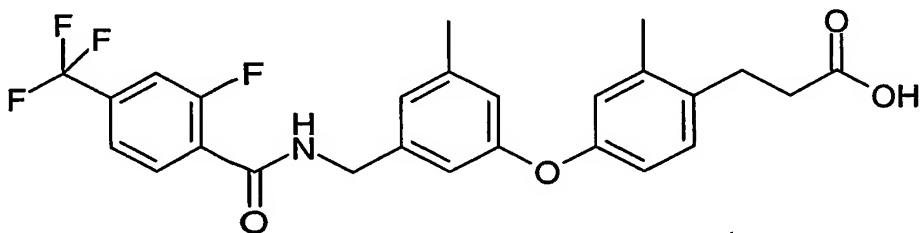
3-[4-(3-[[5-Chloro-3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-methyl]-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-3-methyl-benzo[b]thiophene-2-carboxylic acid and 3-[4-(3-aminomethyl-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 45). Exact mass calcd for  $C_{28}H_{27}ClNO_4S$  ( $M+H^+$ ): 508.1349, found 508.1346;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 201

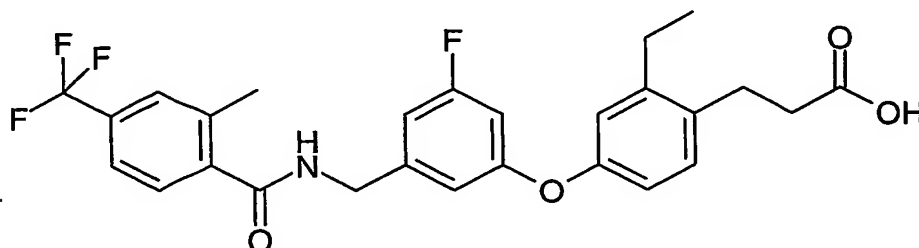
3-(4-{3-[(2-Fluoro-4-trifluoromethyl-benzoylamino)-methyl]-5-methyl-phenoxy}-2-methyl-phenyl)-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 2-fluoro-4-trifluoromethyl-benzoic acid and 3-[4-(3-aminomethyl-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 45). Exact mass calcd for  $C_{26}H_{24}F_4NO_4$  ( $M+H^+$ ): 490.1641, found 490.1645;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 202

3-(2-Ethyl-4-{3-fluoro-5-[(2-methyl-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenyl)-propionic acid

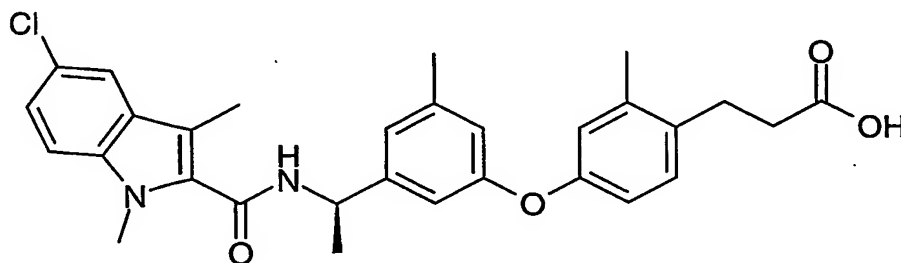


5 The title compound is prepared according to the general procedures described in Example 1 utilizing 2-methyl-4-trifluoromethyl-benzoic acid (Intermediate 10) and 3-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-ethyl-phenyl]-propionic acid ethyl ester (Intermediate 27). Exact mass calcd for  $C_{27}H_{26}NO_4F_4$  ( $M+H^+$ ): 504.1798, found 504.1791;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

10

Example 203

3-[4-(3-{1-[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid

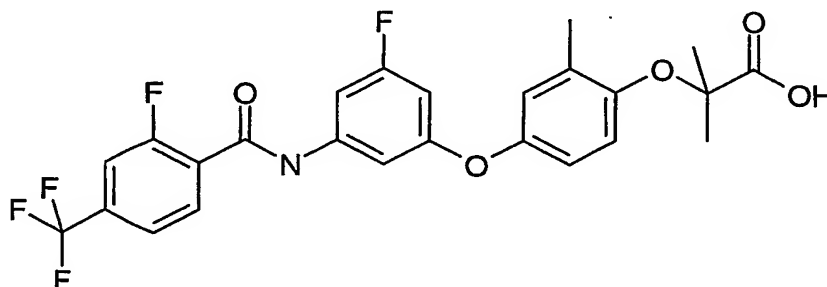


15 The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and 3-{4-[3-(1-amino-ethyl)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester (Intermediate 26). Exact mass calcd for  $C_{30}H_{32}ClN_2O_4$  ( $M+H^+$ ): 519.2051, found 519.2045;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

20

Example 204

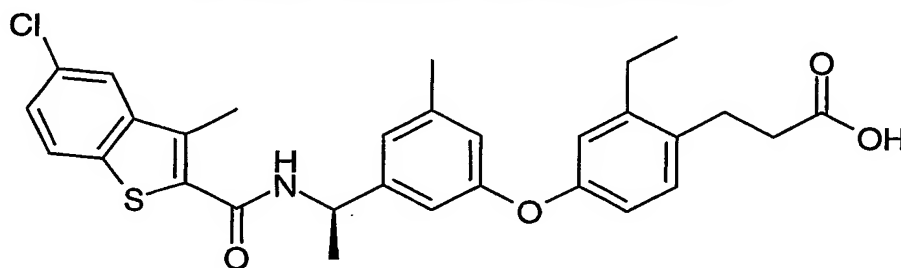
2-{4-[3-Fluoro-5-(2-fluoro-4-trifluoromethyl-benzoylamino)-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 2-fluoro-4-trifluoromethyl-benzoic acid and 2-[4-(3-amino-5-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester (Intermediate 47). Exact mass calcd for  $C_{25}H_{21}F_5NO_5$  ( $M+H^+$ ): 510.1340, found 510.1328;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 205

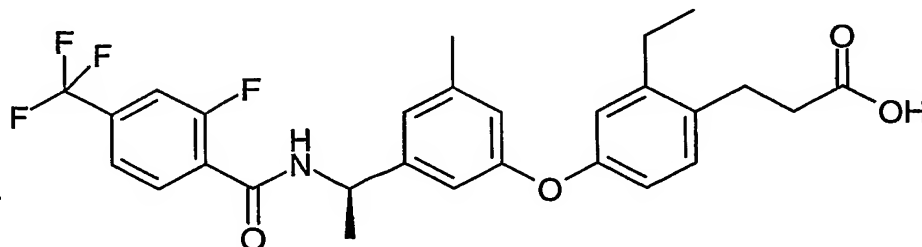
3-[4-(3-{1-[(5-Chloro-3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-ethyl}-5-methyl-phenoxy)-2-ethyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-3-methyl-benzo[b]thiophene-2-carboxylic acid and 3-[4-[3-(1-amino-ethyl)-5-methyl-phenoxy]-2-ethyl-phenyl]-propionic acid ethyl ester (Intermediate 16). Exact mass calcd for  $C_{30}H_{31}ClNO_4S$  ( $M+H^+$ ): 536.1662, found 536.1648;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 206

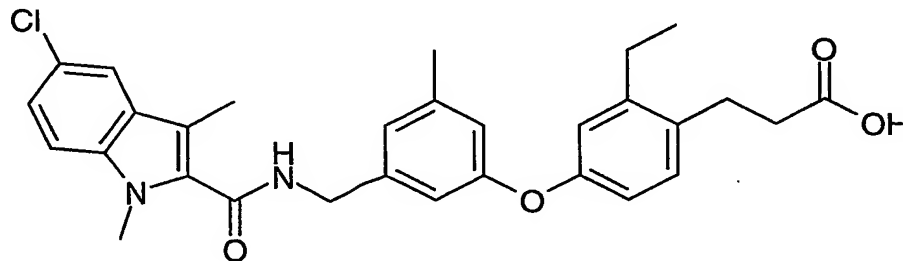
3-(2-Ethyl-4-{3-[1-(2-fluoro-4-trifluoromethyl-benzoylamino)-ethyl]-5-methyl-phenoxy}-phenyl)-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 2-fluoro-4-trifluoromethyl-benzoic acid and 3-{4-[3-(1-amino-ethyl)-5-methyl-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester (Intermediate 16). Exact mass calcd for  $C_{28}H_{28}F_4NO_4$  ( $M+H^+$ ): 518.1954, found 518.1937;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 207

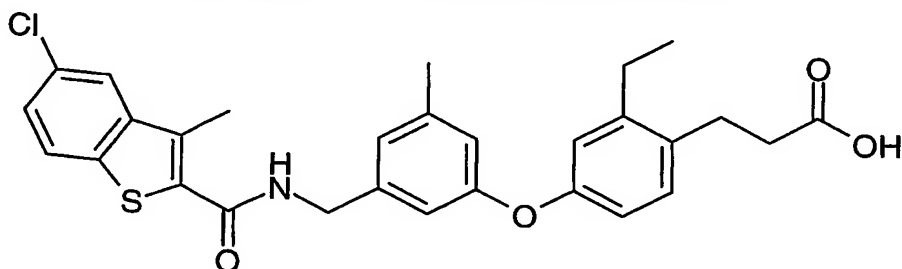
3-[4-(3-[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl)-5-methyl-phenoxy)-2-ethyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and -[4-(3-aminomethyl-5-methyl-phenoxy)-2-ethyl-phenyl]-propionic acid ethyl ester (Intermediate 46). Exact mass calcd for  $C_{30}H_{32}ClN_2O_4$  ( $M+H^+$ ): 519.2051, found 519.2032;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 208

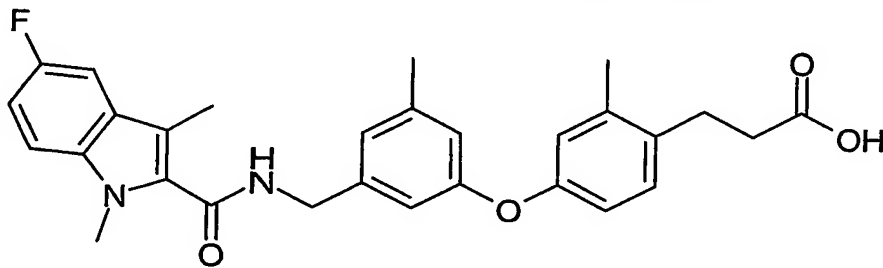
3-[4-(3-[[[(5-Chloro-3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-methyl]-5-methyl-phenoxy)-2-ethyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-chloro-3-methyl-benzo[b]thiophene-2-carboxylic acid and -[4-(3-aminomethyl-5-methyl-phenoxy)-2-ethyl-phenyl]-propionic acid ethyl ester (Intermediate 46). Exact mass calcd for  $C_{29}H_{29}ClNO_4S$  ( $M+H^+$ ): 522.1506, found 522.1502;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 209

3-[4-(3-[[[(5-Fluoro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl]-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid

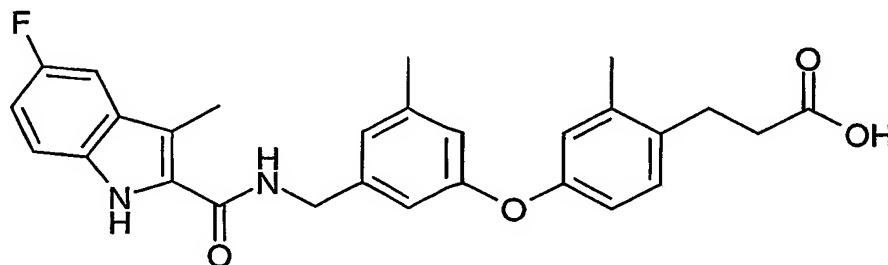


The title compound is prepared according to the general procedures described in Example 1 utilizing 5-fluoro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 2) and 3-[4-(3-aminomethyl-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 45). Exact mass calcd for  $C_{29}H_{30}FN_2O_4$  ( $M+H^+$ ): 489.2190, found 489.2188;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).



Example 210

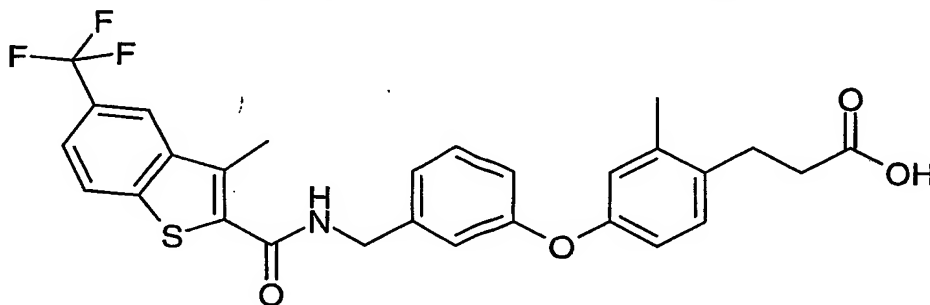
3-[4-(3-[[5-Fluoro-3-methyl-1H-indole-2-carbonyl)-amino]-methyl]-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 5-fluoro-3-methyl-1H-indole-2-carboxylic acid (Intermediate 1) and 3-[4-(3-aminomethyl-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 45). Exact mass calcd for  $C_{28}H_{28}FN_2O_4$  ( $M+H^+$ ): 475.2033, found 475.2020;  $^1H$ NMR (400 MHz,  $CDCl_3$ ).

Example 211

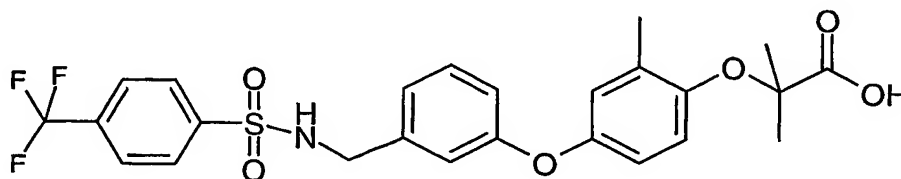
3-[2-Methyl-4-(3-[[3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-carbonyl)-amino]-methyl}-phenoxy)-phenyl]-propionic acid



The title compound is prepared according to the general procedures described in Example 1 utilizing 3-methyl-5-trifluoromethyl-benzo[b]thiophene-2-carboxylic acid (Intermediate 50) and 3-[4-(3-aminomethyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 33).

Example 212

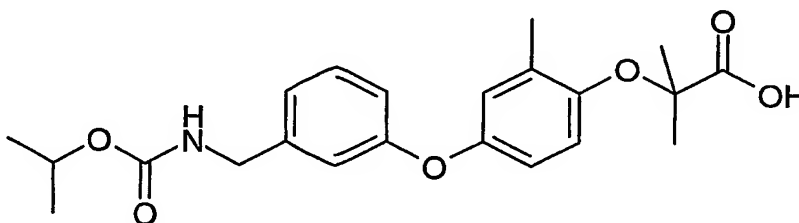
2-Methyl-2-(2-methyl-4-{3-[(4-trifluoromethyl-benzenesulfonylamino)-methyl]-phenoxy}-phenoxy)-propionic acid



The title compound is prepared according to the general procedures described in Example 140 utilizing 4-trifluoromethylbenzenesulfonyl chloride and 2-[4-(3-aminomethylphenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester (Intermediate 17). Mass ( $ES^+$ ): 522.2 ( $M+H^+$ ).

Example 213

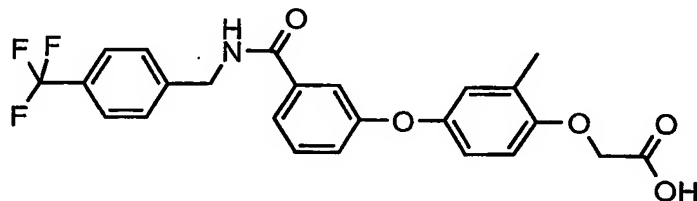
2-{4-[3-(Isopropoxycarbonylamino-methyl)-phenoxy]-2-methyl-phenoxy}-2-methylpropionic acid



The title compound is prepared according to the general procedures described in Example 140 utilizing isopropyl chloroformate and 2-[4-(3-aminomethylphenoxy)-2-methylphenoxy]-2-methylpropionic acid ethyl ester (Intermediate 17). Mass ( $ES^+$ ): 402.3 ( $M+H^+$ ).

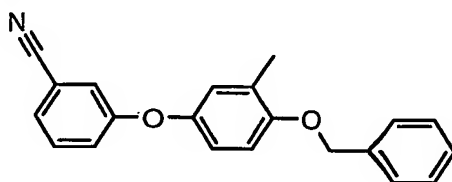
Example 214

{2-Methyl-4-[3-(4-trifluoromethylbenzylcarbamoyl)phenoxy]phenoxy}acetic acid

Step A

5

3-(4-Benzyloxy-3-methylphenoxy)benzonitrile



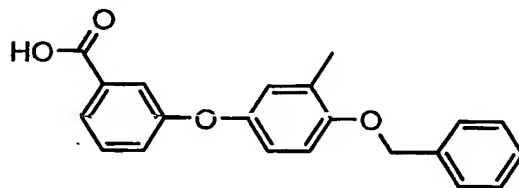
10

A mixture of 4-benzyloxy-3-methylphenol (2.19 g, 10.2 mmol) (prepared substantially the similar way as described in WO9723216), 3-fluorobenzonitrile (1.09 mL, 10.2 mmol), 18-Crown-6 (0.27 g, 1.02 mmol) and 37% potassium fluoride-alumina (3.8 g) (prepared substantially the similar way as described in *Tet Lett*, 32, 7207, (1997)) is stirred in DMSO (25 mL) at 145 °C for about 8 h. The reaction is diluted in 400 mL ether, and the insoluble material is filtered away. The filtrate is washed with brine (3 x 200 mL), dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the title compound as a dark oil (3.1 g, 96%). MS (ES) *m/e* 314 (M-1).

15

Step B

3-(4-Benzyloxy-3-methylphenoxy)benzoic acid



20

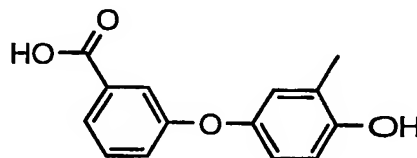
A solution of 3-(4-benzyloxy-3-methylphenoxy)benzonitrile (3.1 g, 9.8 mmol) in methanol (7 mL) and ethanol (10 mL) is treated with KOH pellets (11.0 g, 196.0 mmol). To this slurry is added 30% H<sub>2</sub>O<sub>2</sub>, and the mixture is heated to 100 °C for 2 h. After cooling, the solution is treated with 5N NaOH (30 mL), ether (30mL), and

acidified to pH 1 with conc. HCl (20 mL). The residue is diluted with EtOAc (100 mL) and washed with brine. The organic layer is dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the title compound as a tan solid (3.17 g, 96%). MS (ES) *m/e* 335 (M+1).

5

Step C

3-(4-Hydroxy-3-methylphenoxy)benzoic acid

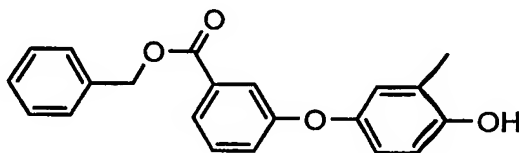


To a solution of 3-(4-benzyloxy-3-methylphenoxy)benzoic acid (3.15 g (9.42 mmol) dissolved in THF (10 mL) and EtOH (50 mL) is treated with 5% Pd/C (0.60 g) and H<sub>2</sub> gas (1 atm) for about 16 h. The catalyst is filtered away, and the filtrate is concentrated and redissolved in MeCl<sub>2</sub> (100 mL). The mixture is washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the title compound as a yellow solid (2.17 g, 94%). MS (ES) *m/e* 243 (M-1).

10

Step D

3-(4-Hydroxy-3-methylphenoxy)benzoic acid benzyl ester

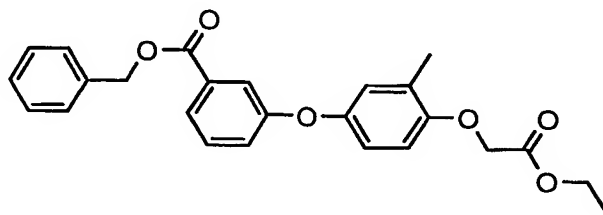


A mixture of 3-(4-hydroxy-3-methylphenoxy)benzoic acid (2.13 g, 8.72 mmol), benzyl bromide (1.35 mL, 11.3 mmol) and cesium carbonate (1.42 g, 4.36 mmol) in DMF (8 mL) is stirred at RT for 16 h. The reaction is concentrated, and the residue is taken up in EtOAc (100 mL), which is then washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, concentrated and purified (radial chromatography, 4 mm plate, 5:95 to 25:75 EtOAc:hex) to give the title compound as a yellow solid (1.70 g, 58%). MS (ES) *m/e* 333 (M-1).

20

Step E

## 3-(4-Ethoxycarbonylmethoxy-3-methylphenoxy)benzoic acid benzyl ester

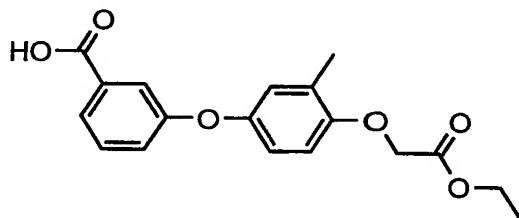


5 A mixture of 3-(4-hydroxy-3-methylphenoxy)benzoic acid benzyl ester (0.85 g, 2.54 mmol), ethylbromoacetate (0.65 mL, 5.08 mmol) and cesium carbonate (1.65 g, 5.08 mmol) in DMF (6 mL) is stirred at RT for 2 h. The reaction is concentrated, and the residue is taken up in EtOAc (100 mL), which is then washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, concentrated and purified (radial chromatography, 2 mm plate, 5:95 to 15:85 EtOAc:hex) to give the title compound as a colorless oil (0.82 g, 76%). MS (ES) *m/e* 438 (M+NH<sub>4</sub>).

10

Step F

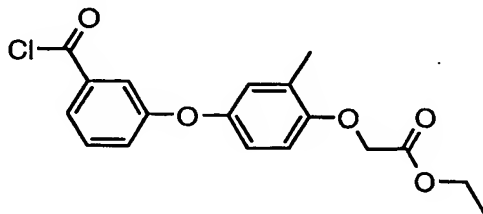
## 3-(4-Ethoxycarbonylmethoxy-3-methylphenoxy)benzoic acid



15 A mixture of 3-(4-ethoxycarbonylmethoxy-3-methylphenoxy)benzoic acid benzyl ester (0.80 g, 1.90 mmol) in EtOH (200 mL) is treated with 5% Pd/C (0.19 g) and H<sub>2</sub> gas (60 psi) at RT for about 4.5 h. The catalyst is filtered, and the filtrate is concentrated to give the title compound as a white solid (0.61 g, 96%). MS (ES) *m/e* 348 (M+NH<sub>4</sub>).

Step G

[4-(3-Chlorocarbonylphenoxy)-2-methylphenoxy]acetic acid ethyl ester



To a solution of 3-(4-ethoxycarbonylmethoxy-3-methylphenoxy)benzoic acid (0.61 g, 1.84 mmol) in MeCl<sub>2</sub> (30 mL) is added oxalyl chloride (0.95 mL, 11.1 mmol) and one drop of DMF. The solution is stirred for 4 h at RT and concentrated to give the title compound as a pale yellow oil (0.61 g, 95%), which is used directly in the next step.

Step H-I

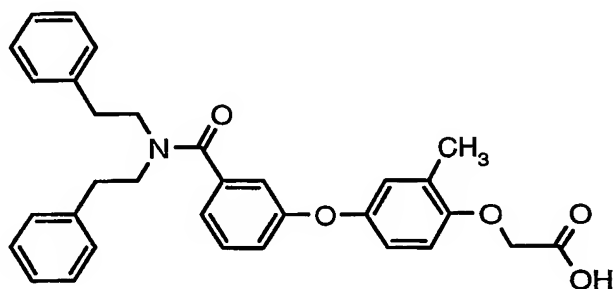
{2-Methyl-4-[3-(4-trifluoromethylbenzylcarbamoyl)phenoxy]phenoxy}acetic acid

A solution of 4-trifluoromethylbenzylamine (0.031 mL, 0.24 mmol) and Et<sub>3</sub>N (0.033 mL, 0.24 mmol) in MeCl<sub>2</sub> (1 mL) is treated with [4-(3-chlorocarbonylphenoxy)-2-methylphenoxy]acetic acid ethyl ester (0.040 g, 0.11 mmol) in 1 mL MeCl<sub>2</sub>. The reaction is stirred at RT for 2.5 h and concentrated. The residue is treated with EtOH (1 mL), THF (0.5 mL) and 2N NaOH (0.30 mL, 0.60 mmol) and heated at 50 °C for 16 h. After cooling, the reaction is concentrated and diluted with 20 mL MeCl<sub>2</sub> and 20 mL water and acidified to pH 1 using 1N HCl. The organic layer is washed with brine and concentrated. The crude residue is purified using mass-directed reverse phase HPLC to give the title compound as a white solid (0.013 g, 25%. MS (ES) *m/e* 460 (M+1).

Examples 215 to 219 are prepared in the substantially the similar way as described in Example 214.

Example 215

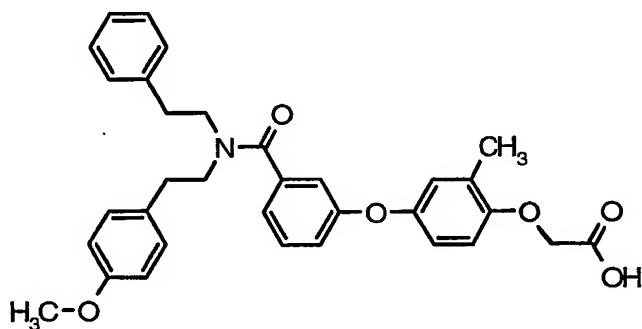
[4-(3-Diphenethylcarbamoylphenoxy)-2-methylphenoxy]acetic acid



5           The title compound is prepared by using diphenethylamine, which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES) *m/e* 510 (M+1).

Example 216

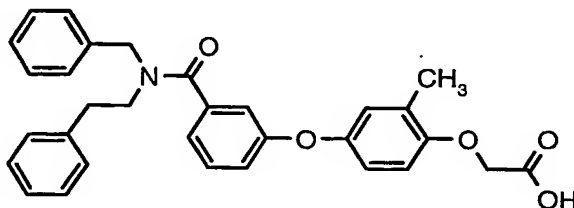
10       [4-(3-{[2-(4-Methoxyphenyl)ethyl]phenethylcarbamoyl}phenoxy)-2-methylphenoxy]acetic acid



15       The title compound is prepared by using [2-(4-methoxyphenyl)ethyl]phenethylamine, which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES) *m/e* 540 (M+1).

Example 217

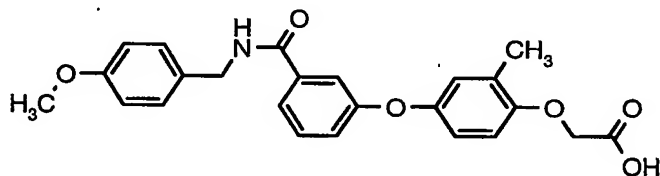
{4-[3-(Benzylphenethylcarbamoyl)phenoxy]-2-methylphenoxy}acetic acid



The title compound is prepared by using commercially available  
5 benzylphenethylamine. MS (ES) *m/e* 496 (M+1).

Example 218

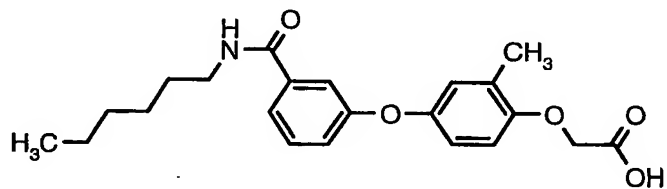
{4-[3-(4-Methoxybenzylcarbamoyl)phenoxy]-2-methylphenoxy}acetic acid



10 The title compound is prepared by using commercially available 4-methoxybenzylamine. MS (ES) *m/e* 422 (M+1).

Example 219

[4-(3-Hexylcarbamoylphenoxy)-2-methylphenoxy]acetic acid



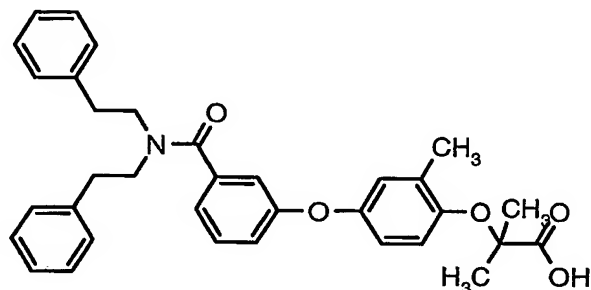
15 The title compound is prepared by using commercially available n-hexylamine. MS (ES) *m/e* 386 (M+1).

Example 220 to 254 are prepared substantially the similar way as described in Example 214 except that ethyl 2-bromoisobutyrate is used in Example 214,  
20 Step E.



Example 220

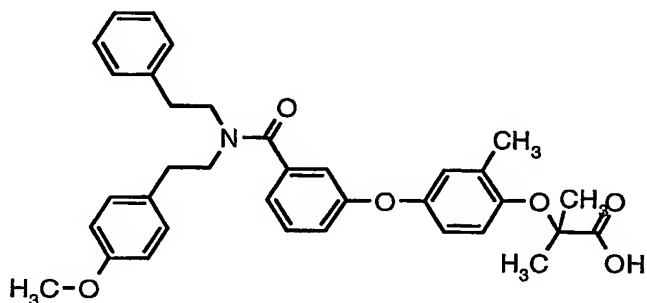
2-[4-(3-Diphenethylcarbamoylphenoxy)-2-methylphenoxy]-2-methylpropionic acid



The title compound is prepared by using diphenethylamine, which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES) *m/e* 538 (M+1).

Example 221

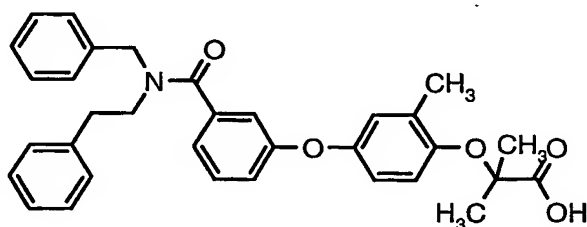
2-[4-(3-{[2-(4-Methoxyphenyl)ethyl]phenethylcarbamoyl}phenoxy)-2-methylphenoxy]-2-methylpropionic acid



The title compound is prepared by using [2-(4-methoxyphenyl)ethyl]phenethylamine which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES) *m/e* 554 (M+1).

Example 222

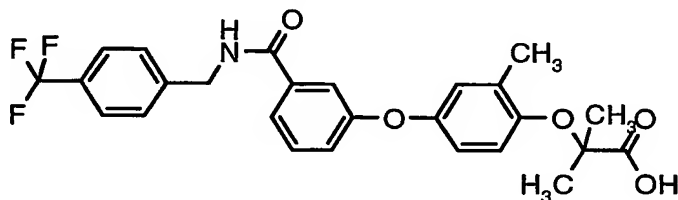
2-{4-[3-(Benzylphenethylcarbamoyl)phenoxy]-2-methylphenoxy}-2-methylpropionic acid



The title compound is prepared by using the commercially available benzylphenethylamine. MS (ES)  $m/e$  524 (M+1).

Example 223

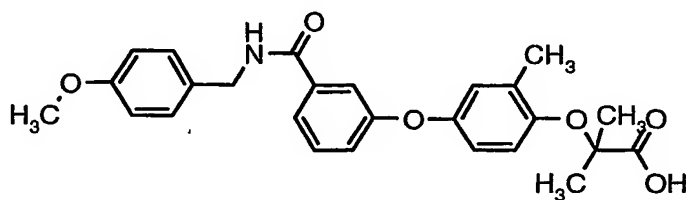
2-Methyl-2-{2-methyl-4-[3-(4-trifluoromethylbenzylcarbamoyl)phenoxy]phenoxy} propionic acid



The title compound is prepared by using the commercially available 4-trifluoromethylbenzylamine. MS (ES)  $m/e$  488 (M+1).

Example 224

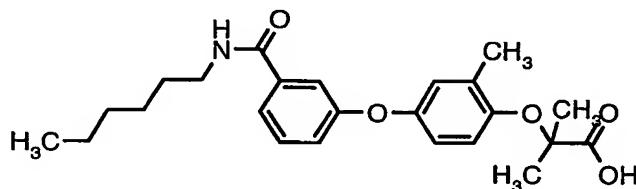
2-{4-[3-(4-Methoxybenzylcarbamoyl)phenoxy]-2-methylphenoxy}-2-methylpropionic acid,



The title compound is prepared by using the commercially available 4-methoxybenzylamine. MS (ES)  $m/e$  450 (M+1).

Example 225

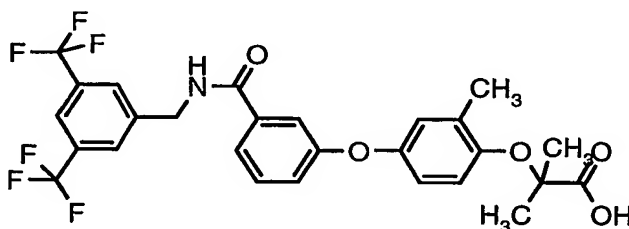
2-[4-(3-Hexylcarbamoylphenoxy)-2-methylphenoxy]-2-methylpropionic acid



The title compound is prepared by using the commercially available n-hexylamine. MS (ES) *m/e* 414 (M+1).

Example 226

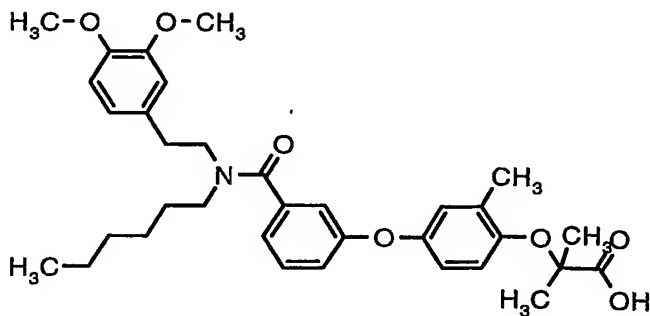
2-{4-[3-(3,5-Bistrifluoromethylbenzylcarbamoyl)phenoxy]-2-methylphenoxy}-2-methylpropionic acid



The title compound is prepared by using the commercially available 3,5-trifluoromethylbenzylamine. MS (ES) *m/e* 556 (M+1).

Example 227

2-[4-(3-{[2-(3,4-Dimethoxyphenyl)ethyl]hexylcarbamoyl}phenoxy)-2-methylphenoxy]-2-methylpropionic acid

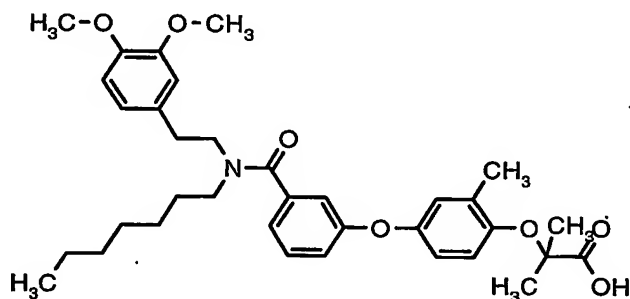


The title compound is prepared by using [2-(3,4-dimethoxyphenyl)ethyl]heptylamine which may be prepared essentially as described in Example 258, Steps A and B. MS (ES) *m/e* 578 (M+1).

5

Example 228

2-[4-(3-{[2-(3,4-Dimethoxyphenyl)ethyl]heptylcarbamoyl}phenoxy)-2-methylphenoxy]-2-methylpropionic acid

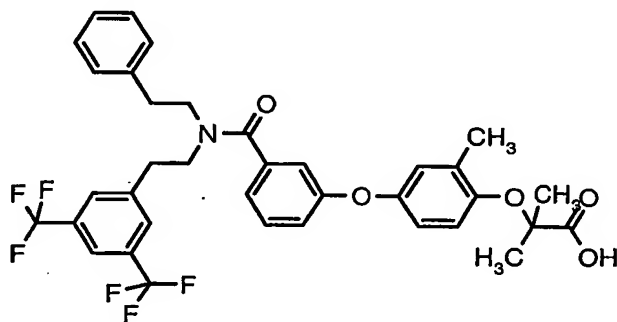


The title compound is prepared by using [2-(3,4-dimethoxyphenyl)ethyl]heptylamine which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES) *m/e* 592 (M+1).

15

Example 229

2-[4-(3-{[2-(3,5-Bistrifluoromethyl)phenyl]ethyl]phenethylcarbamoyl}phenoxy)-2-methylphenoxy]-2-methylpropionic acid

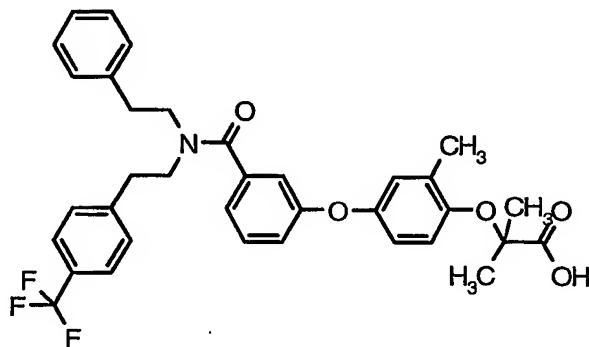


The title compound is prepared by using [2-(3,5-bistrifluoromethyl)phenyl]ethyl]phenethylamine which is prepared substantially the similar way described in Example 258, Steps A and B. MS (ES) *m/e* 674 (M+1).

20

Example 230

2-Methyl-2-[2-methyl-4-(3-{phenethyl-[2-(4-trifluoromethylphenyl)ethyl]carbamoyl}phenoxy)phenoxy]propionic acid



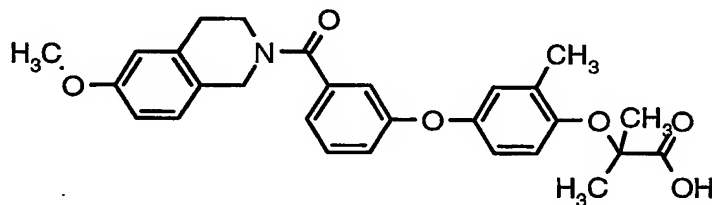
5

The title compound is prepared by using [2-(4-trifluoromethylphenyl)ethyl]phenethylamine, which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES) *m/e* 606 (M+1).

10

Example 231

2-{4-[3-(6-Methoxy-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]-2-methylphenoxy}-2-methylpropionic acid

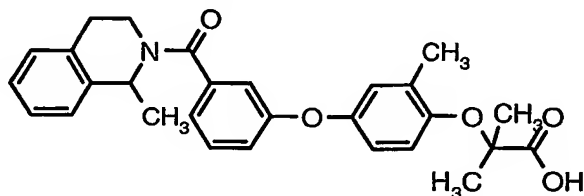


The title compound is prepared by using 6-methoxy-1,2,3,4-tetrahydroisoquinoline which is prepared substantially the similar way as described in JACS, 56, 1769-1771 (1934). MS (ES) *m/e* 476 (M+1).

15

Example 232

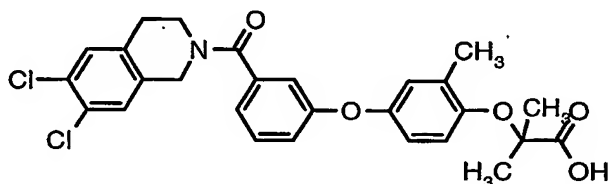
2-Methyl-2-{2-methyl-4-[3-(1-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]  
phenoxy}propionic acid



5           The title compound is prepared by using 1-methyl-1,2,3,4-tetrahydroisoquinoline, which is prepared substantially the similar way as described in *J. Chem. Soc. Perkin Trans.1*, 9, 955-977 (2001). MS (ES) *m/e* 460 (M+1).

Example 233

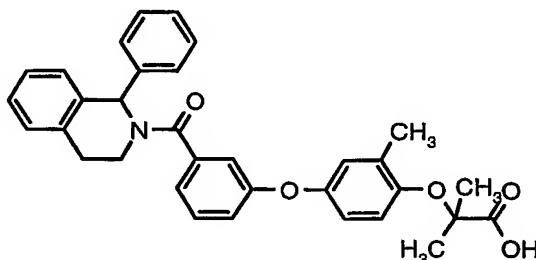
10           2-{4-[3-(6,7-Dichloro-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]-2-methylphenoxy}-2-methylpropionic acid



15           The title compound is prepared by using 6,7-dichloro-1,2,3,4-tetrahydroisoquinoline, which is prepared substantially the similar way as described in *Tet. Lett.*, 21, 1393-1396 (1980). MS (ES) *m/e* 515 (M+1).

Example 234

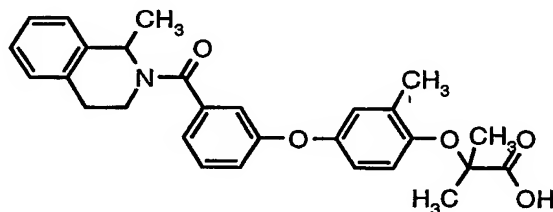
2-Methyl-2-{2-methyl-4-[3-(1-phenyl-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]  
phenoxy}propionic acid



5 The title compound is prepared by using 1-phenyl-1,2,3,4-tetrahydroisoquinolin, which is prepared substantially the similar way as described in *Chem. Ber.*, 91, 1133-1138 (1958). MS (ES) *m/e* 522 (M+1).

Example 235

10 2-Methyl-2-{2-methyl-4-[3-(1-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]  
phenoxy}propionic acid

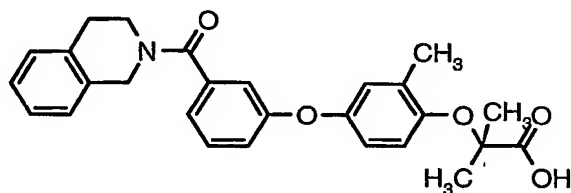


The title compound is prepared by using 1-methyl-1,2,3,4-tetrahydroisoquinoline, which is prepared substantially the similar way as described in *J. Chem. Soc. Perkin Trans.1*, 2, 955-977 (2001). MS (ES) *m/e* 460 (M+1).

15

Example 236

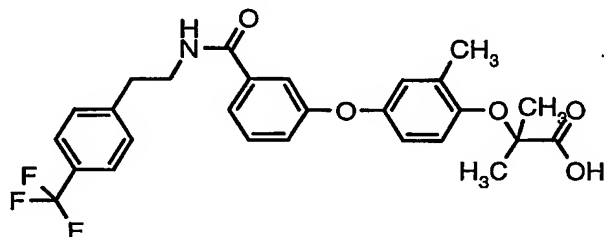
2-{4-[3-(3,4-Dihydro-1H-isoquinoline-2-carbonyl)phenoxy]-2-methylphenoxy}-2-methylpropionic acid



5 The title compound is prepared by using the commercially available 1,2,3,4-tetrahydroisoquinoline. MS (ES) *m/e* 446 (M+1).

Example 237

2-Methyl-2-(2-methyl-4-{3-[2-(4-trifluoromethylphenyl)ethylcarbamoyl]phenoxy}phenoxy)propionic acid

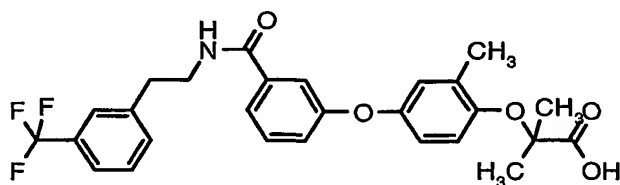


The title compound is prepared by using the commercially available 4-trifluoromethylphenethylamine. MS (ES) *m/e* 502 (M+1).

15

Example 238

2-Methyl-2-(2-methyl-4-{3-[2-(3-trifluoromethylphenyl)ethylcarbamoyl]phenoxy}phenoxy) propionic acid

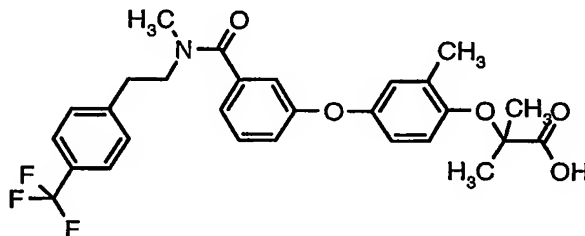


20 The title compound is prepared by using the commercially available 3-trifluoromethylphenethylamine. MS (ES) *m/e* 502 (M+1).



Example 239

2-Methyl-2-[2-methyl-4-(3-{methyl-[2-(3-trifluoromethylphenyl)ethyl]carbamoyl} phenoxy) phenoxy]propionic acid



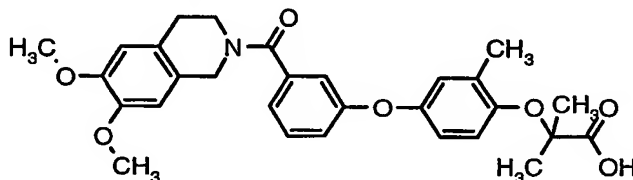
5

The title compound is prepared by using methyl[2-(4-trifluoromethylphenyl) ethyl]amine, which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES) *m/e* 516 (M+1).

10

Example 240

2-{4-[3-(6,7-Dimethoxy-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]-2-methylphenoxy}-2-methylpropionic acid

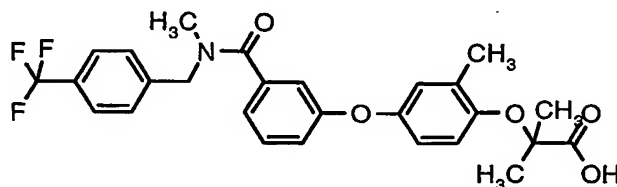


15

The title compound is prepared by using 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, which is prepared substantially the similar way as described in *JACS*, 56, 1769-1771 (1934), MS (ES) *m/e* 506 (M+1).

Example 241

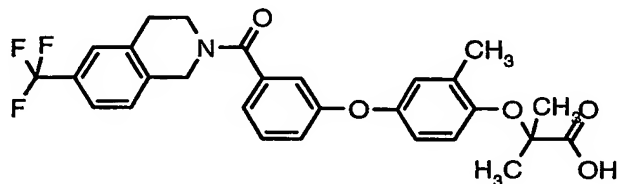
2-Methyl-2-(2-methyl-4-{3-[methyl-(4-trifluoromethylbenzyl)carbamoyl]phenoxy}  
phenoxy)propionic acid



5 The title compound is prepared by using methyl(4-trifluoromethylbenzyl)amine which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES) *m/e* 502 (M+1).

Example 242

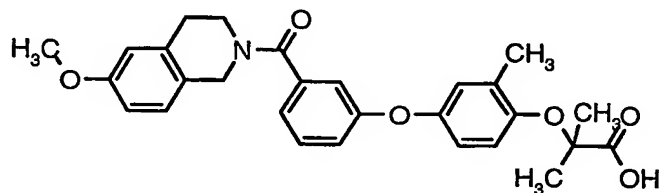
10 2-Methyl-2-{2-methyl-4-[3-(6-trifluoromethyl-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]phenoxy}propionic acid



The title compound is prepared by using 6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline, which is prepared substantially the similar way as described in  
15 WO 9850364. MS (ES) *m/e* 515 (M+1).

Example 243

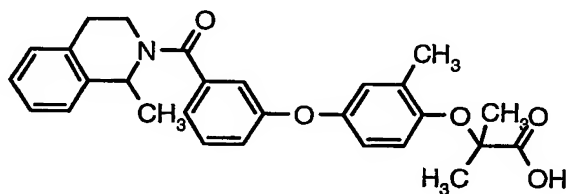
2-{4-[3-(6-Methoxy-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]-2-methylphenoxy}-2-methylpropionic acid



5 The title compound is prepared by using 6-methoxy-1,2,3,4-tetrahydroisoquinoline, which is prepared substantially the similar way as described in *JACS*, 56, 1769-1771 (1934). MS (ES) *m/e* 476 (M+1).

Example 244

10 2-Methyl-2-{2-methyl-4-[3-(1-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]phenoxy}propionic acid

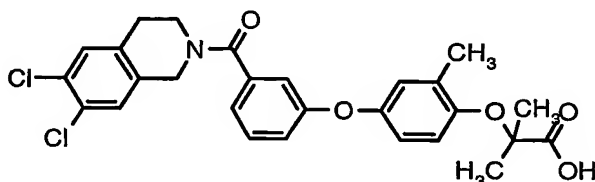


The title compound is prepared by using 1-methyl-1,2,3,4-tetrahydroisoquinoline, which is prepared substantially the similar way as described in *J. Chem. Soc. Perkin Trans.1*, 9, 955-977 (2001). MS (ES) *m/e* 460 (M+1).

15

Example 245

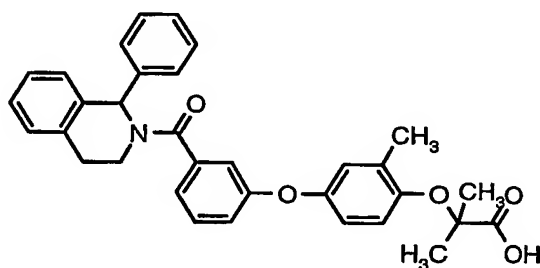
2-{4-[3-(6,7-Dichloro-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]-2-methylphenoxy}-2-methylpropionic acid



5 The title compound is prepared by using 6,7-dichloro-1,2,3,4-tetrahydroisoquinoline, which is prepared substantially the similar way as described in *Tet. Lett.*, 21, 1393-1396 (1980). MS (ES) *m/e* 515 (M+1).

Example 246

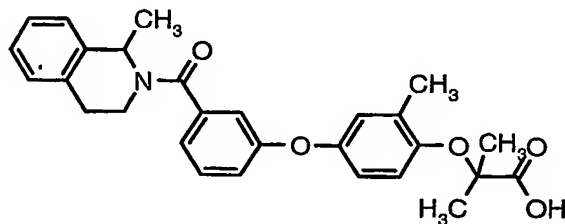
10 2-Methyl-2-{2-methyl-4-[3-(1-phenyl-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]phenoxy}propionic acid



The title compound is prepared by using 1-phenyl-1,2,3,4-tetrahydroisoquinoline, which is prepared substantially the similar way as described in  
15 *Chem. Ber.*, 91, 1133-1138 (1958). MS (ES) *m/e* 522 (M+1).

Example 247

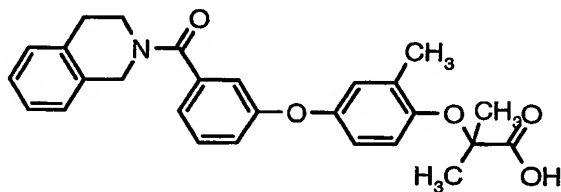
2-Methyl-2-{2-methyl-4-[3-(1-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]phenoxy}propionic acid



5           The title compound is prepared by using 1-methyl-1,2,3,4-tetrahydroisoquinoline, which is prepared substantially the similar way as described in *J. Chem. Soc. Perkin Trans.1*, 2, 955-977 (2001). MS (ES) *m/e* 460 (M+1).

Example 248

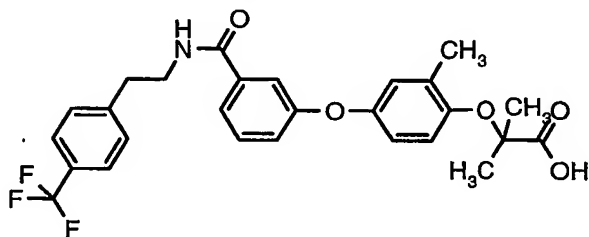
10       2-{4-[3-(3,4-Dihydro-1H-isoquinoline-2-carbonyl)phenoxy]-2-methylphenoxy}-2-methylpropionic acid



15           The title compound is prepared by using the commercially available 1,2,3,4-tetrahydroisoquinoline. MS (ES) *m/e* 446 (M+1).

### Example 249

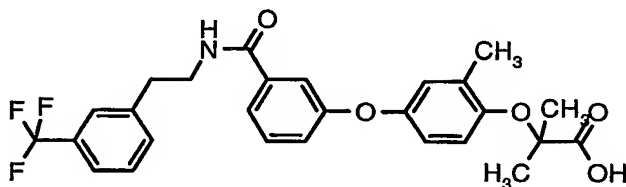
2-Methyl-2-(2-methyl-4-{3-[2-(4-trifluoromethylphenyl)ethylcarbonyl]phenoxy}  
phenoxy)propionic acid



The title compound is prepared by using the commercially available 4-trifluoromethylphenethylamine. MS (ES) *m/e* 502 (M+1).

### Example 250

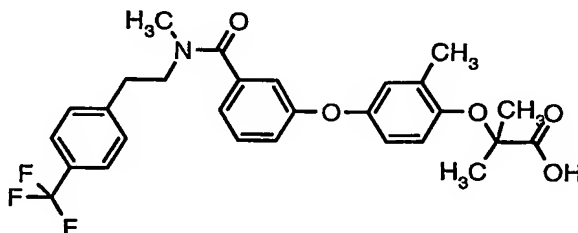
2-Methyl-2-(2-methyl-4-{3-[2-(3-trifluoromethylphenyl)ethylcarbonyl]phenoxy}  
phenoxy)propionic acid



The title compound is prepared by using the commercially available 3-trifluoromethylphenethylamine. MS (ES) *m/e* 502 (M+1).

Example 251

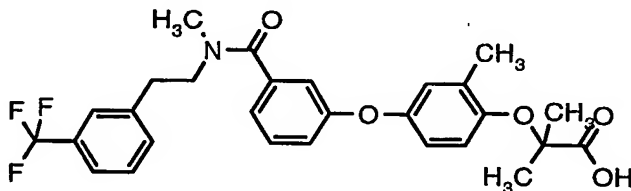
2-Methyl-2-[2-methyl-4-(3-{methyl-[2-(4-trifluoromethylphenyl)ethyl]carbamoyl}phenoxy)phenoxy]propionic acid



The title compound is prepared by using methyl(4-trifluoromethylphenyl)ethylamine, which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES) *m/e* 516 (M+1).

Example 252

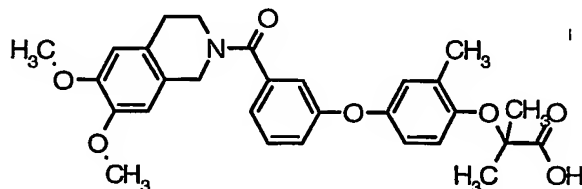
2-Methyl-2-[2-methyl-4-(3-{methyl-[2-(3-trifluoromethylphenyl)ethyl]carbamoyl}phenoxy)phenoxy]propionic acid



The title compound is prepared by using methyl(3-trifluoromethylphenyl)ethylamine, which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES) *m/e* 516 (M+1).

Example 253

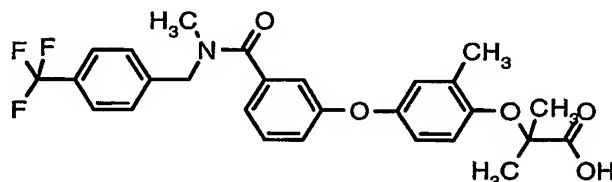
2-{4-[3-(6,7-Dimethoxy-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]-2-methylphenoxy}-2-methylpropionic acid



5 The title compound is prepared by using 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, which is prepared substantially the similar way as described in *JACS*, 56, 1769-1771 (1934). MS (ES) *m/e* 506 (M+1).

Example 254

10 2-Methyl-2-(2-methyl-4-{3-[methyl-(4-trifluoromethylbenzyl)carbamoyl]phenoxy}phenoxy)propionic acid

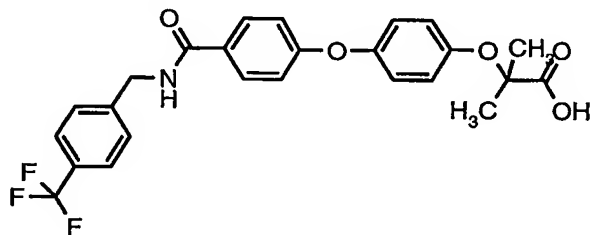


The title compound is prepared by using methyl(4-trifluoromethylbenzyl)amine, which is prepared substantially the similar way as described  
15 in Example 258, Steps A and B. MS (ES) *m/e* 502 (M+1).



Example 255

2-Methyl-2-{4-[4-(4-trifluoromethylbenzylcarbamoyl)phenoxy]phenoxy}propionic acid

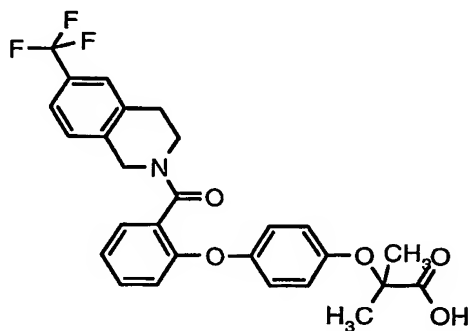


The title compound is prepared by using the commercially available 4-trifluoromethylbenzylamine and following the procedure described in Example 214 except that the synthesis begins with Example 214, Step C using the commercially available 4-(4-hydroxyphenoxy)benzoic acid and ethyl 2-bromoisobutyrate in Example 214, Step E. MS (ES) *m/e* 474 (M+1).

Examples 256 to 257 are prepared as described in Example 214 except that 2-fluorobenzonitrile is used in Example 214, Step A and ethyl 2-bromoisobutyrate is used in Example 214, Step E.

Example 256

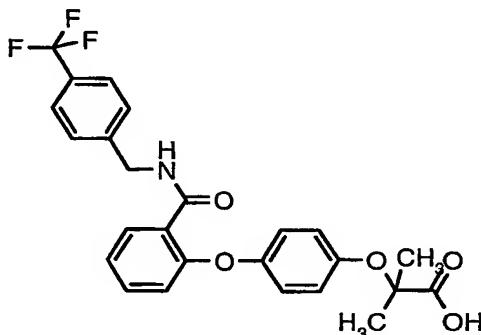
2-Methyl-2-{4-[2-(6-trifluoromethyl-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]phenoxy}propionic acid



The title compound is prepared by using 6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline, which is prepared substantially the similar way as described in WO 9850364. MS (ES) *m/e* 500 (M+1).

Example 257

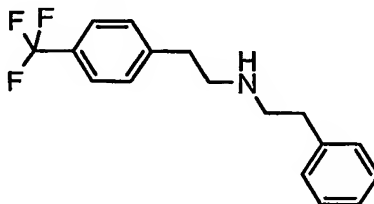
2-Methyl-2-{4-[2-(4-trifluoromethylbenzylcarbamoyl)phenoxy]phenoxy}propionic acid



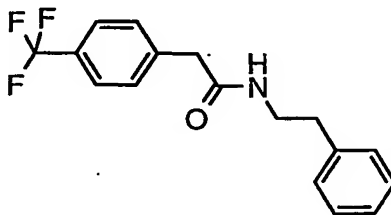
The title compound is prepared by using the commercially available 4-trifluoromethylbenzylamine. MS (ES) *m/e* 474 (M+1).

Example 258

Phenethyl[2-(4-trifluoromethylphenyl)ethyl]amine

Step A

N-Phenethyl-2-(4-trifluoromethylphenyl)acetamide

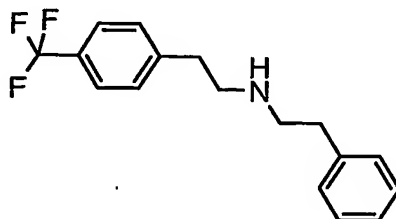


To a solution of 4-trifluoromethylphenylacetic acid (3.0 g, 14.7 mmol) in MeCl<sub>2</sub> (30 mL) is added oxalyl chloride (7.6 mL, 88.2 mmol) with 3 drops of DMF, and the mixture is stirred at RT for 5 h. The reaction is concentrated, and the crude acid chloride is redissolved in MeCl<sub>2</sub> (15 mL) and added dropwise to an ice bath cooled solution of phenethylamine (2.3 mL, 18.4 mmol) and Et<sub>3</sub>N (4.1 mL, 30 mmol) in MeCl<sub>2</sub>

(15 mL). The reaction is stirred at RT for about 16 h and diluted with 50 mL MeCl<sub>2</sub> and 100 mL water, which is then acidified to pH 1 using 1N HCl. The organic layer is washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, concentrated, and purified (radial chromatography, 4 mm plate, 15:85 to 25:75 EtOAc:hex) to give the title compound as a pale yellow solid (2.57 g, 56% over 2 steps). MS (ES) *m/e* 308 (M+1).

#### Step B

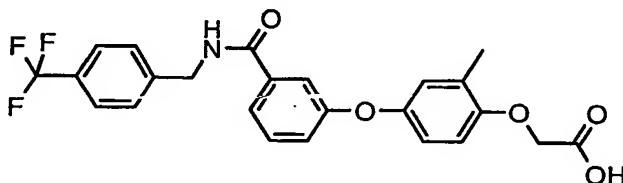
Phenethyl[2-(4-trifluoromethylphenyl)ethyl]amine



To a mixture of lithium borohydride (0.73 g, 33.5 mmol) and trimethylsilyl chloride (8.1 mL, 64.4 mmol) in THF (15 mL) is added a solution of N-phenethyl-2-(4-trifluoromethylphenyl)acetamide (2.54 g, 6.77 mmol) in THF (15 mL). The reaction is stirred for about 56 h (40 h RT, 16 h at 50 °C). After cooling, the reaction is treated slowly with 20 mL MeOH and concentrated. The residue is taken up in MeCl<sub>2</sub> (150 ml) and washed with water (100 mL), and then treated with 5N NaOH to bring the pH to about 12. The organic layer is washed with water, dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give the title compound as a yellow oil. MS(ES) *m/e* 294 (M+1).

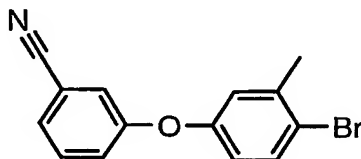
#### Example 259

3-{2-Methyl-4-[3-(4-trifluoromethylbenzylcarbamoyl)phenoxy]phenyl}propionic acid



Step A

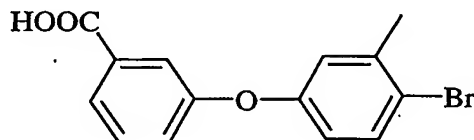
3-(4-Bromo-3-methylphenoxy)benzonitrile



5 This compound is prepared following the procedure of Example 214, Step A except that commercially available 4-bromo-3-methylphenol is used. MS (ES) *m/e* 306 (M+NH<sub>4</sub>).

Step B

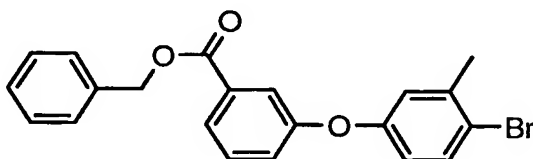
3-(4-Bromo-3-methylphenoxy)benzoic acid



10 This compound is prepared as described in Example 214, Step B. MS (ES) *m/e* 305 (M-1).

Step C

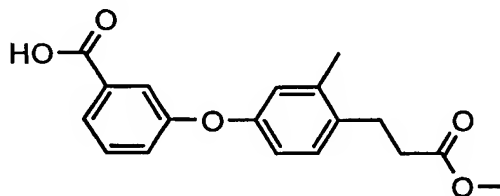
3-(4-Bromo-3-methylphenoxy)benzoic acid benzyl ester



15 This compound is prepared as described in Example 214, Step D. MS (ES) *m/e* 397 (M+1).

Steps D-E

## 3-[4-(2-Methoxycarbonylethyl)-3-methylphenoxy]benzoic acid

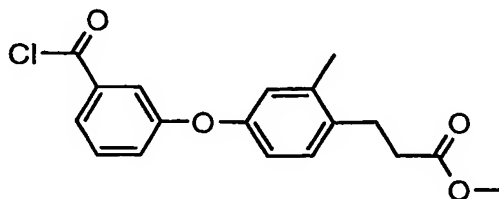


The compound of 3-(4-bromo-3-methylphenoxy)benzoic acid benzyl ester  
5 (10.4 g, 26.1 mmol) in propionitrile (200 mL) is treated with DIPEA (10.5 mL, 60.3 mmol). The mixture is degassed (3x vacuum/N<sub>2</sub> purge), and methyl acrylate (11 mL, 120 mmol) is added. The mixture is degassed (1x), and tri-*o*-tolylphosphine (3.65 g, 12.0 mmol) and Pd(OAc)<sub>2</sub> are added. The mixture is degassed (2x), heated at 110 °C for 2.5 h, cooled, filtered, and concentrated. The crude product is purified (silica gel  
10 chromatography, hex:EtOAc 100:0 to 80:20) to give 3-[4-(2-methoxycarbonylvinyl)-3-methylphenoxy]benzoic acid benzyl ester as a yellow oil (9.76 g).

The oily material is dissolved in MeOH (200 mL) and treated with 5% Pd/C (1.25 g) and H<sub>2</sub> gas (60 psi) at RT overnight. The mixture is filtered and concentrated. The product mixture is purified (silica gel chromatography,  
15 hex:EtOAc:HOAc 3:1:0 to 1:1:0.02) to give 3-[4-(2-methoxycarbonylvinyl)-3-methylphenoxy]benzoic acid. This material is dissolved in MeOH (125 mL) and treated with 5% Pd/C (5 g) and H<sub>2</sub> gas (60 psi) at RT 16 h. The mixture is filtered and concentrated. The crude product is purified (silica gel chromatography, hex:EtOAc:HOAc 3:1:0 to 1:1:0.02) to give the title compound (1.8 g, 22%). MS (ES)  
20 *m/e* 313 (M-1).

Step F

3-[4-(3-Chlorocarbonylphenoxy)-2-methylphenyl]propionic acid methyl ester



The title compound is prepared according to the procedure described in

5 Example 214, Step G.

Steps G-H

3-{2-Methyl-4-[3-(4-trifluoromethylbenzylcarbamoyl)phenoxy]phenyl}propionic acid

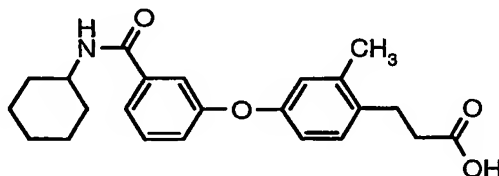
The title compound is prepared according to the procedure described in

Example 214, Steps H-I. MS(ES) *m/e* 458 (M+1).

10 Examples 260 and 281 are prepared substantially the similar way as described in Example 259.

Example 260

3-[4-(3-Cyclohexylcarbamoylphenoxy)-2-methylphenyl]propionic acid

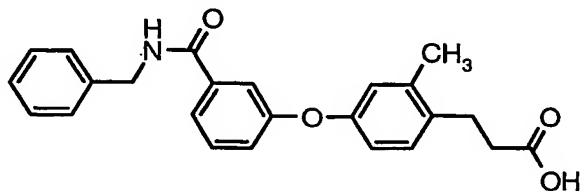


15

The title compound is prepared by using the commercially available cyclohexylamine. MS (ES) *m/e* 382 (M+1).

Example 261

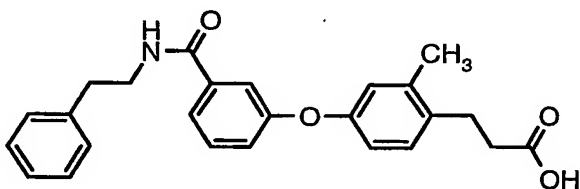
3-[4-(3-Benzylcarbamoylphenoxy)-2-methylphenyl]propionic acid



5 The title compound is prepared by using the commercially available benzylamine. MS (ES) *m/e* 390 (M+1).

Example 262

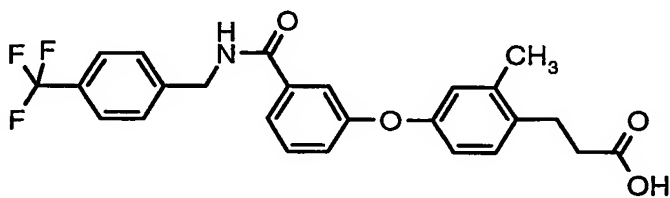
3-[2-Methyl-4-(3-phenethylcarbamoylphenoxy)phenyl]propionic acid



10 The title compound is prepared by using commercially available phenethylamine. MS (ES) *m/e* 404 (M+1).

Example 263

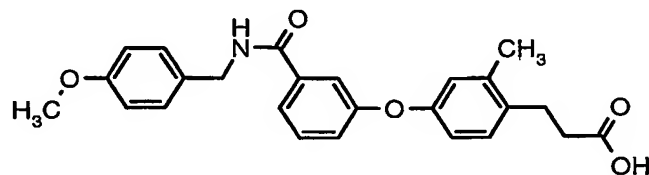
3-[2-Methyl-4-(3-phenethylcarbamoylphenoxy)phenyl]propionic acid



15 The title compound is prepared by using commercially available 4-trifluoromethylbenzylamine. MS (ES) *m/e* 458 (M+1).

Example 264

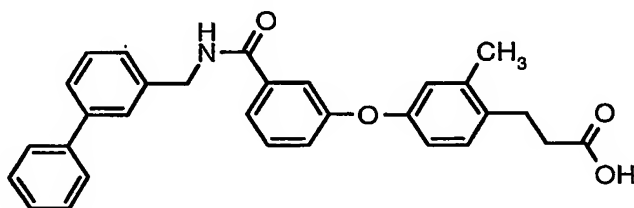
3-{ 4-[3-(4-Methoxybenzyl)carbamoyl]phenoxy]-2-methylphenyl}propionic acid



The title compound is prepared by using commercially available 4-methoxybenzylamine. MS (ES) *m/e* 420 (M+1).

Example 265

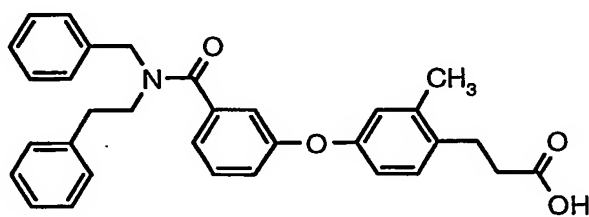
3-(4-{ 3-[(Biphenyl-3-ylmethyl)carbamoyl]phenoxy}-2-methylphenyl)propionic acid



The title compound is prepared by using commercially available biphenyl-3-ylmethylamine. MS (ES) *m/e* 466 (M+1).

Example 266

3-{ 4-[3-(Benzylphenethyl)carbamoyl]phenoxy]-2-methylphenyl}propionic acid

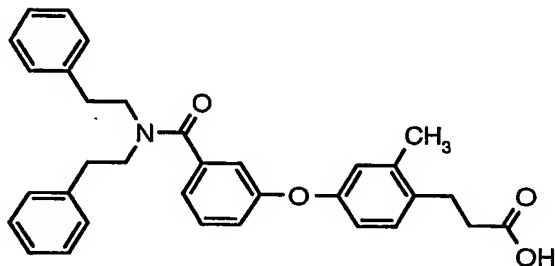


The title compound is prepared by using commercially available benzylphenethylamine. MS (ES) *m/e* 494 (M+1).



Example 267

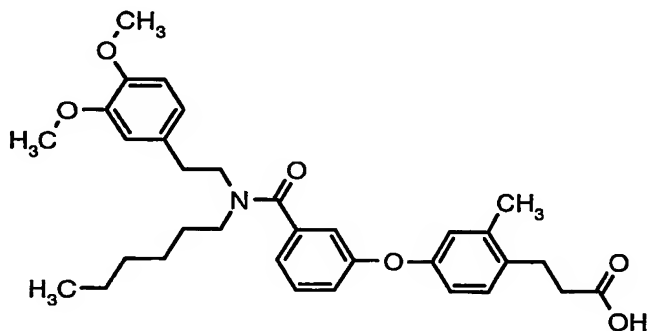
3-[4-(3-Diphenethylcarbamoylphenoxy)-2-methylphenyl]propionic acid



The title compound is prepared by using diphenethylamine, which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES) *m/e* 508 (M+1).

Example 268

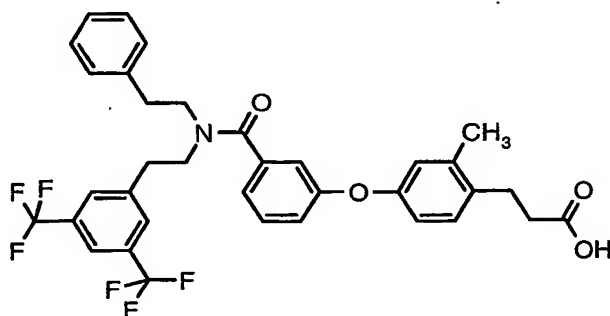
3-[4-(3-{[2-(3,4-Dimethoxyphenyl)ethyl]hexylcarbamoyl}phenoxy)-2-methylphenyl]propionic acid



The title compound is prepared by using [2-(3,4-dimethoxyphenyl)ethyl]heptylamine, which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES) *m/e* 548 (M+1).

Example 269

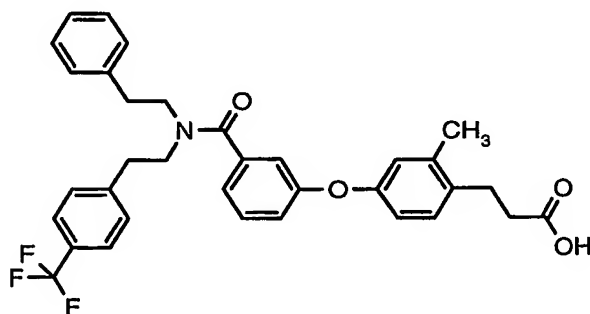
3-[4-(3-{[2-(3,5-Bis-trifluoromethylphenyl)ethyl]phenethylcarbamoyl}phenoxy)-2-methylphenyl]propionic acid



5 The title compound is prepared by using [2-(3,5-bis(trifluoromethyl)phenyl)ethyl] phenethylamine which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES) *m/e* 644 (M+1).

Example 270

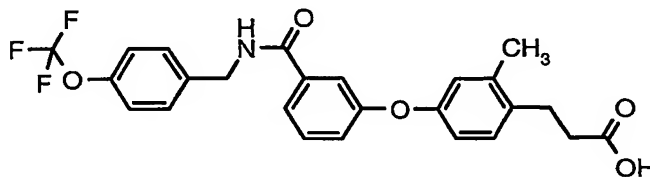
10 3-[2-Methyl-4-(3-{phenethyl[2-(4-trifluoromethylphenyl)ethyl]carbamoyl}phenoxy)phenyl] propionic acid



15 The title compound is prepared by using [2-(4-trifluoromethylphenyl)ethyl] phenethylamine, which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES) *m/e* 576 (M+1).

Example 271

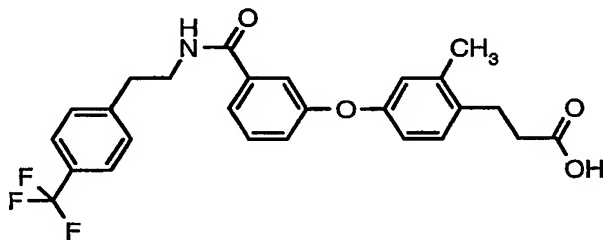
3-{2-Methyl-4-[3-(4-trifluoromethoxybenzylcarbamoyl)phenoxy]phenyl}propionic acid



The title compound is prepared by using the commercially available 4-trifluoromethoxybenzylamine. MS (ES)  $m/e$  474 (M+1).

Example 272

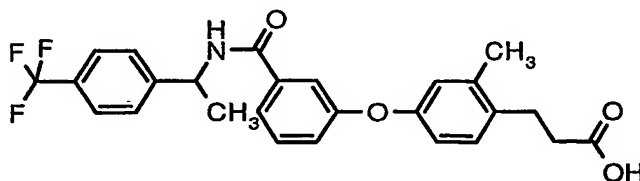
3-(2-Methyl-4-{3-[2-(4-trifluoromethylphenyl)ethylcarbamoyl]phenoxy}phenyl)propionic acid



The title compound is prepared by using the commercially available 4-trifluoromethylphenethylamine. MS (ES)  $m/e$  472 (M+1).

Example 273

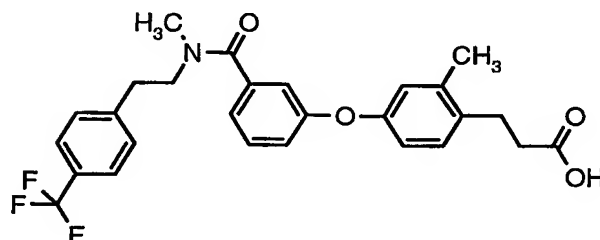
3-(2-Methyl-4-{3-[1-(4-trifluoromethylphenyl)ethylcarbamoyl]phenoxy}phenyl)propionic acid



The title compound is prepared by using 1-(4-trifluoromethylphenyl)ethylamine, which is prepared substantially the similar way as described in *J. Med. Chem.*, 10, 873-840 (1967). MS (ES)  $m/e$  472 (M+1).

Example 274

3-[2-Methyl-4-(3-{methyl-[2-(4-trifluoromethylphenyl)ethyl]carbamoyl}phenoxy)  
phenyl]propionic acid



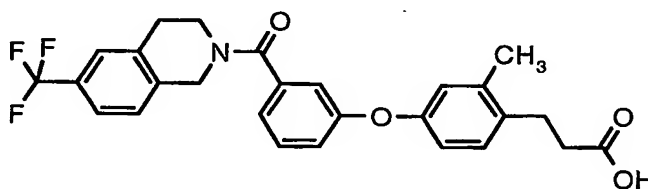
5

The title compound is prepared by using methyl(4-trifluoromethylphenyl) ethylamine, which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES) *m/e* 486 (M+1).

10

Example 275

3-[2-Methyl-4-[3-(6-trifluoromethyl-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]  
phenyl]propionic acid

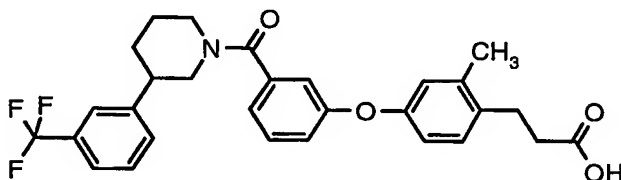


The title compound is prepared by using 6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline, which is prepared substantially the similar way as described in WO 9850364. MS (ES) *m/e* 617 (M+1).

15

Example 276

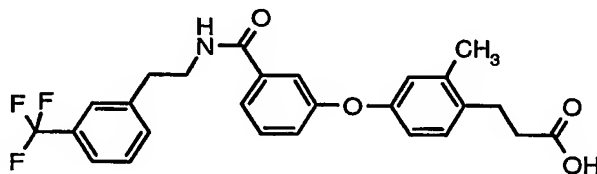
3-(2-Methyl-4-{3-[3-(3-trifluoromethylphenyl)piperidine-1-carbonyl]phenoxy}phenyl)  
propionic acid



5 The title compound is prepared by using 3-(3-trifluoromethylphenyl)piperidine, which is prepared substantially the similar way as described in *J. Med. Chem.*, 30, 2169-2174 (1987). MS (ES) *m/e* 512 (M+1).

Example 277

10 3-(2-Methyl-4-{3-[2-(3-trifluoromethylphenyl)ethylcarbamoyl]phenoxy}phenyl)  
propionic acid

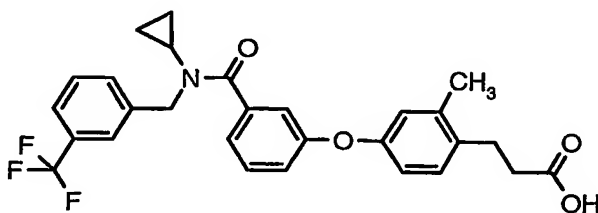


The title compound is prepared by using the commercially available 3-trifluoromethylphenethylamine. MS (ES) *m/e* 472 (M+1).

15

Example 278

3-(4-{3-[Cyclopropyl-(3-trifluoromethylbenzyl)carbamoyl]phenoxy}-2-methylphenyl)  
propionic acid



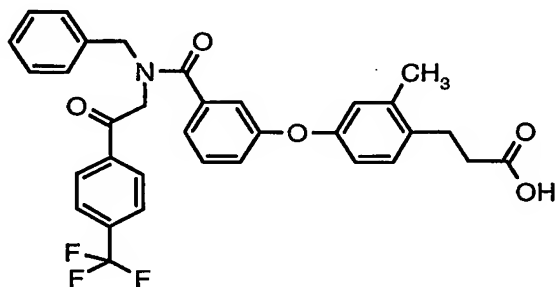
20

The title compound is prepared by using cyclopropyl(3-trifluoromethylbenzyl)amine which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES) *m/e* 498 (M+1).

5

Example 279

3-[4-(3-{Benzyl-[2-oxo-2-(4-trifluoromethylphenyl)ethyl]carbamoyl}phenoxy)-2-methylphenyl]propionic acid

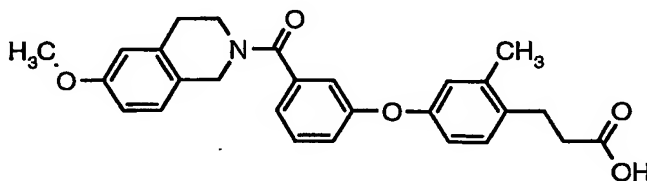


The title compound is prepared by using 2-benzylamino-1-(4-trifluoromethylphenyl)ethanone which is prepared substantially the similar way as described in Example 258, Step A. MS (ES) *m/e* 576 (M+1).

10

Example 280

3-[4-[3-(6-Methoxy-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]-2-methylphenyl]propionic acid

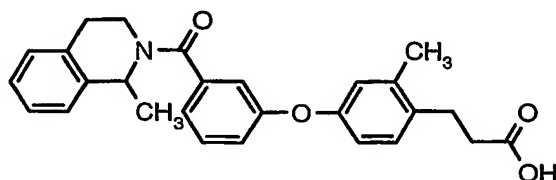


The title compound is prepared by using 6-methoxy-1,2,3,4-tetrahydroisoquinoline, which is prepared substantially the similar way as described in JACS, 56, 1769-1771 (1934). MS (ES) *m/e* 446 (M+1).

20

Example 281

3-{2-Methyl-4-[3-(1-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]  
phenyl}propionic acid



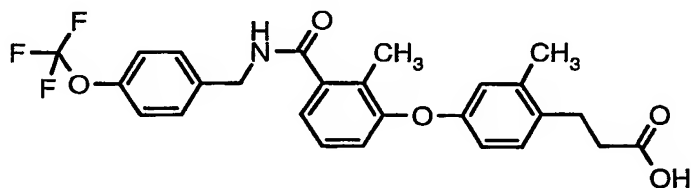
5 The title compound is prepared by using 1-methyl-1,2,3,4-tetrahydroisoquinoline, which is prepared substantially the similar way as described in *J. Chem. Soc. Perkin Trans.1*, 9, 955-977 (2001). MS (ES) *m/e* 430 (M+1).

Examples 282 to 292 are prepared according to the procedure described in Example 259 except that 3-fluoro-2-methylbenzonitrile is used in Example 259, Step A.

10 The compound of 3-fluoro-2-methylbenzonitrile is prepared substantially the similar way as described in US 6,063,789

Example 282

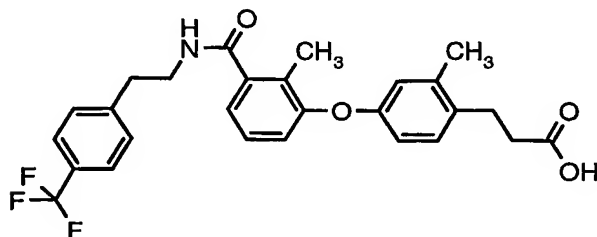
15 3-{2-Methyl-4-[2-methyl-3-(4-trifluoromethoxybenzylcarbamoyl)phenoxy]phenyl}  
propionic acid



The title compound is prepared by using the commercially available trifluoromethoxybenzylamine. MS (ES) *m/e* 488 (M+1).

Example 283

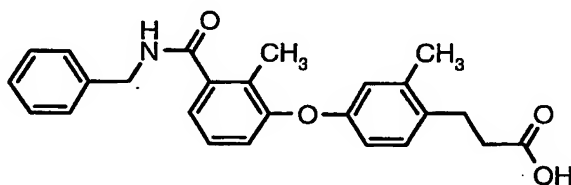
3-(2-Methyl-4-{2-methyl-3-[2-(4-trifluoromethylphenyl)ethylcarbamoyl]phenoxy}phenyl)propionic acid



5 The title compound is prepared by using the commercially available 4-trifluoromethylphenethylamine. MS (ES) *m/e* 486 (M+1).

Example 284

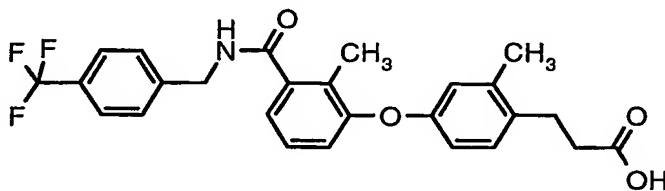
3-[4-(3-Benzylcarbamoyl-2-methylphenoxy)-2-methylphenyl]propionic acid



10 The title compound is prepared by using the commercially available benzylamine. MS (ES) *m/e* 404 (M+1).

Example 285

3-{2-Methyl-4-[2-methyl-3-(4-trifluoromethylbenzylcarbamoyl)phenoxy]phenyl}propionic acid

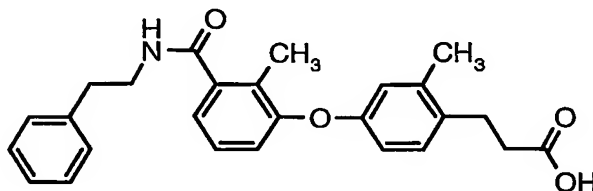


20 The title compound is prepared by using the commercially available 4-trifluoromethylbenzylamine. MS (ES) *m/e* 472 (M+1).



Example 286

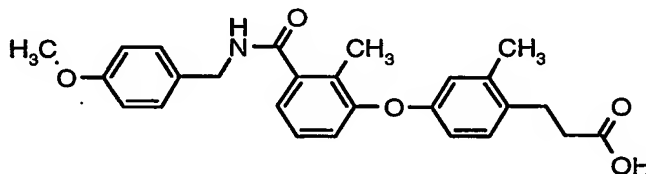
3-[2-Methyl-4-(2-methyl-3-phenethylcarbamoylphenoxy)phenyl]propionic acid



5 The title compound is prepared by using the commercially available phenethylamine. MS (ES) *m/e* 418 (M+1).

Example 287

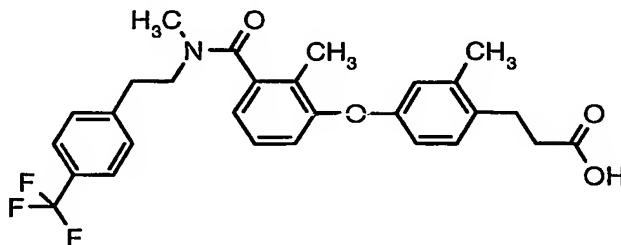
3-{4-[3-(4-Methoxybenzylcarbamoyl)-2-methylphenoxy]-2-methylphenyl}propionic acid



10 The title compound is prepared by using the commercially available 4-methoxybenzylamine. MS (ES) *m/e* 434 (M+1).

Example 288

15 3-[2-Methyl-4-(2-methyl-3-{methyl-[2-(4-trifluoromethylphenyl)ethyl]carbamoyl}phenoxy)phenyl]propionic acid

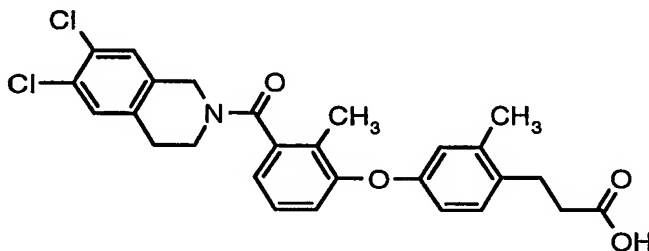


The title compound is prepared by using methyl(4-trifluoromethylphenyl)ethylamine which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES) *m/e* 500 (M+1).

20

Example 289

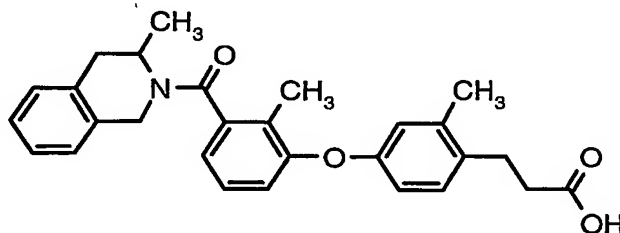
3-{4-[3-(6,7-Dichloro-3,4-dihydro-1H-isoquinoline-2-carbonyl)-2-methylphenoxy]-2-methylphenyl}propionic acid



The title compound is prepared by using 6,7-dichloro-1,2,3,4-tetrahydroisoquinoline which is prepared substantially the similar way as described in *Tet. Lett.*, 21, 1393-1396 (1980). MS (ES) *m/e* 499 (M+1).

Example 290

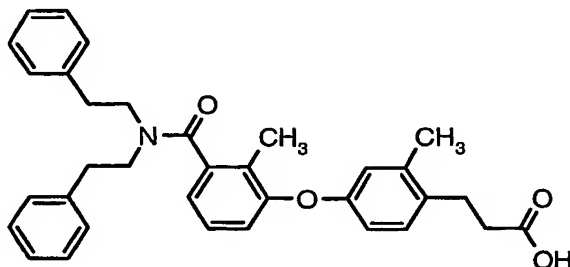
3-{2-Methyl-4-[2-methyl-3-(3-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]phenyl}propionic acid



The title compound is prepared by using 3-methyl-1,2,3,4-tetrahydroisoquinoline, which is prepared substantially the similar way as described in *J. Chem. Soc. Perkin Trans.1*, 9, 955-977 (2001). MS (ES) *m/e* 444 (M+1).

Example 291

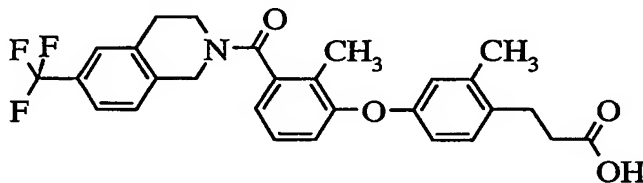
3-[4-(3-Diphenethylcarbamoyl-2-methylphenoxy)-2-methylphenyl]propionic acid



The title compound is prepared by using diphenethylamine, which is prepared substantially the similar way as described in Example 258, Steps A and B. MS (ES)  $m/e$  522 ( $M+1$ ).

Example 292

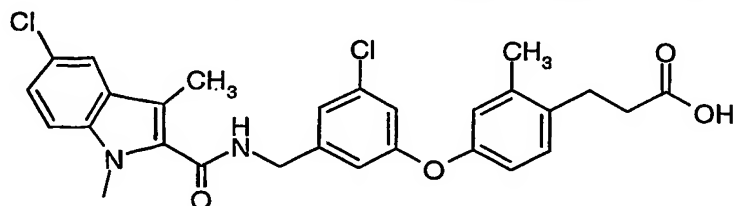
3-{2-Methyl-4-[2-methyl-3-(6-trifluoromethyl-3,4-dihydro-1H-isoquinoline-2-carbonyl)phenoxy]phenyl}propionic acid



The title compound is prepared by using 6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline, which is prepared substantially the similar way as described in WO 9850364. MS (ES)  $m/e$  498 ( $M+1$ ).

Example 293

3-[4-(3-Chloro-5-[[[(5-chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl]-phenoxy)-2-methyl-phenyl]-propionic acid

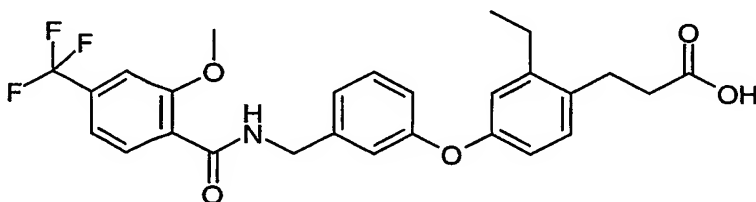


5 The title compound is prepared according to Example 1 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and 3-[4-(3-aminomethyl-5-chloro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester (Intermediate 61). Exact mass calcd for  $C_{28}H_{27}Cl_2N_2O_4$  ( $M+H^+$ ): 525.1348, found 525.1332;  $^1H$  NMR (400 MHz, DMSO- $D_6$ ).

10

Example 294

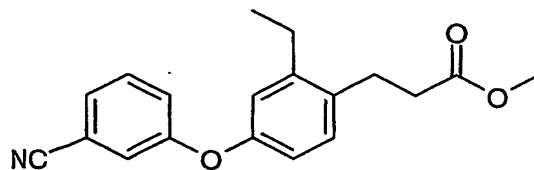
3-(2-Ethyl-4-{3-[(2-methoxy-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenyl)-propionic acid



15

Step A

3-[4-(3-Cyano-phenoxy)-2-ethyl-phenyl]-propionic acid methyl ester



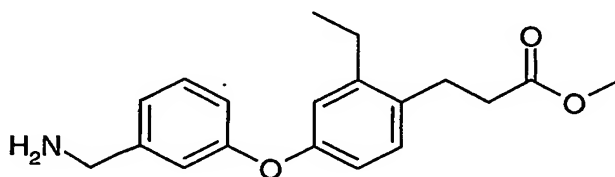
20

A mixture of 3-bromobenzonitrile (1.3 g, 7.2 mmol), 3-(2-ethyl-4-hydroxy-phenyl)-propionic acid methyl ester (0.5 g, 2.4 mmol), copper (I) chloride (0.12 g, 1.2 mmol), cesium carbonate (1.6 g, 4.8 mmol), and 2,2,6,6-tetramethyl-3,5-heptanedione (0.12 mL, 0.6 mmol) in NMP (10 mL) is purged with nitrogen. The

reaction is heated to 120 °C and stirred overnight. The reaction is cooled to room temperature and filtered through celite. The filtrate is quenched with 1N aqueous HCl and extracted with diethyl ether. The organic is washed with brine, dried over sodium sulfate, filtered and the solvent is removed. The crude product is purified by silica gel column chromatography using 4/1 Hexanes/Ethyl acetate to elute the pure product. The solvent is removed to afford about 0.375 g (50%) of desired product. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>19</sub>H<sub>19</sub>NO<sub>3</sub> 309, found 310 (M + 1).

### Step B

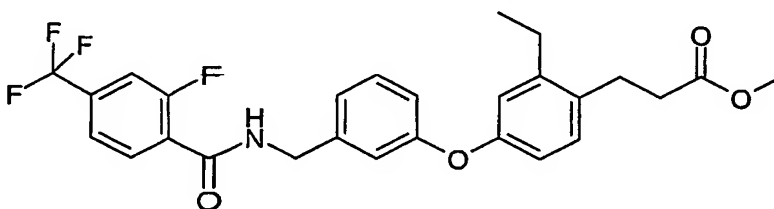
3-[4-(3-Aminomethyl-phenoxy)-2-ethyl-phenyl]-propionic acid methyl ester



A solution of 3-[4-(3-cyano-phenoxy)-2-ethyl-phenyl]-propionic acid methyl ester (0.38 g, 1.2 mmol) and 5% palladium on carbon (40 mg) in acetic acid (50 mL) is purged with hydrogen (60 psi). The reaction stirred at room temperature overnight. The reaction is filtered through celite and the filtrate is concentrated to one-quarter volume. The solution is quenched with saturate aqueous sodium bicarbonate solution. The aqueous is extracted with diethyl ether. The organic is washed with brine, dried over sodium sulfate, filtered and the solvent is removed to afford about 0.28 g (74%) of desired product. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>19</sub>H<sub>23</sub>NO<sub>3</sub> 313, found 314 (M + 1, 100%).

### Step C

3-(2-Ethyl-4-{3-[(2-fluoro-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenyl)-propionic acid methyl ester



A solution of 3-[4-(3-aminomethyl-phenoxy)-2-ethyl-phenyl]-propionic acid methyl ester (0.28 g, 0.9 mmol), 2-fluoro-4-(trifluoromethyl)benzoic acid (0.22 g,

1.07 mmol), 1-hydroxybenzotriazole hydrate (0.15 g, 1.07 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.21 g, 1.07 mmol) and N,N-diisopropylethylamine (0.16 mL, 0.9 mmol) is combined in THF (10 mL). The reaction stirred overnight at room temperature. The reaction is quenched with 1N aqueous HCl and extracted with diethyl ether. The organic is washed with brine, dried over sodium sulfate, filtered and the solvent is removed. The crude is purified by silica gel column chromatography using 4/1 (Hexanes/Ethyl acetate) to elute the pure product. The solvent is removed to afford about 0.24 g (53%) of desired product. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>27</sub>H<sub>25</sub>F<sub>4</sub>NO<sub>4</sub> 503, found 504 (M + 1, 100%).

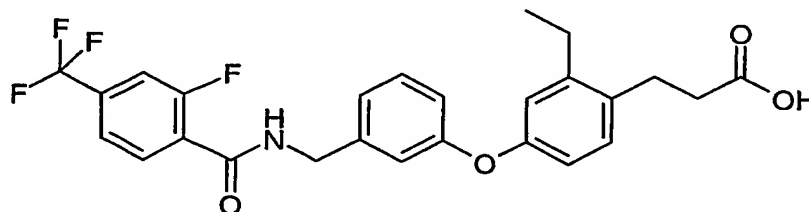
#### Step D

3-(2-Ethyl-4-{3-[(2-methoxy-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenyl)-propionic acid

A solution of 3-(2-ethyl-4-{3-[(2-fluoro-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenyl)-propionic acid methyl ester (0.24 g, 0.5 mmol) in methanol (10 mL) is treated with 5N aqueous sodium hydroxide (0.9 mL). The reaction is heated to reflux and stirred for 1 hour. The reaction is quenched with 1N aqueous HCl and extracted with diethyl ether. The organic is washed with brine, dried over sodium sulfate, and filtered. The solvent is removed to afford about 0.2 g (83%) of desired product. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>27</sub>H<sub>26</sub>F<sub>3</sub>NO<sub>5</sub> 501, found 502 (M + 1, 100%).

#### Example 295

3-(2-Ethyl-4-{3-[(2-fluoro-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenyl)-propionic acid

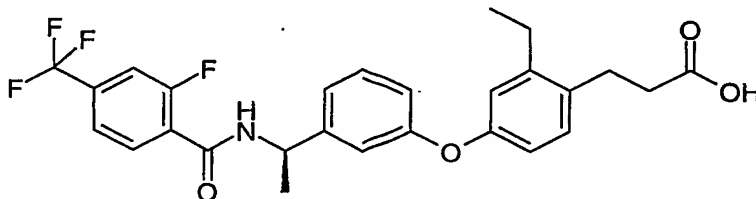


A solution of 3-(2-ethyl-4-{3-[(2-fluoro-4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-phenyl)-propionic acid methyl ester (0.81 g, 1.6 mmol) in dioxane (10

mL) is treated with 1N aqueous lithium hydroxide (16 mL). The reaction is stirred overnight at room temperature. The reaction is quenched with 1N aqueous HCl and extracted with diethyl ether. The organic is washed with brine, dried over sodium sulfate, and filtered. The solvent is removed to afford about 0.65 g (82%) of desired product. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>26</sub>H<sub>23</sub>F<sub>4</sub>NO<sub>4</sub> 489, found 490 (M + 1, 100%).

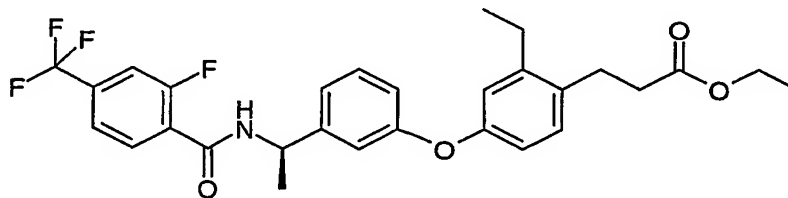
### Example 296

(R)-3-(2-Ethyl-4-{3-[1-(2-fluoro-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenyl)-propionic acid



### Step A

(R)-3-(2-Ethyl-4-{3-[1-(2-fluoro-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenyl)-propionic acid ethyl ester



The procedure from Example 294, Step C is utilized with (R)-3-{4-[3-(1-amino-ethyl)-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester to afford about 0.43 g (80%) of desired product. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>29</sub>H<sub>29</sub>F<sub>4</sub>NO<sub>4</sub> 531, found 532 (M + 1, 100%).

### Step B

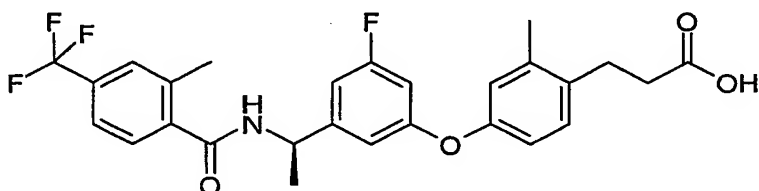
(R)-3-(2-Ethyl-4-{3-[1-(2-fluoro-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenyl)-propionic acid

The procedure from Example 295 is utilized with (R)-3-(2-ethyl-4-{3-[1-(2-fluoro-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenyl)-propionic acid ethyl

ester to afford about 0.23 g (57%) of desired product.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ); MS ( $\text{ES}^+$ )  $m/z$  mass calcd for  $\text{C}_{27}\text{H}_{25}\text{F}_4\text{NO}_4$  503, found 504 ( $M + 1$ , 100%).

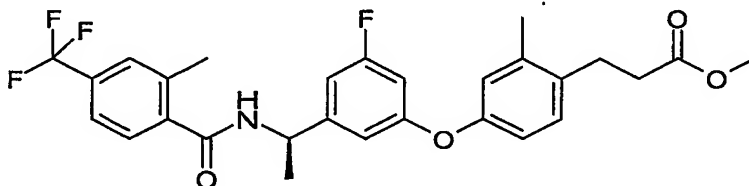
### Example 297

- 5 (R)-3-(4-{3-Fluoro-5-[1-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid



### Step A

- 10 (R)-3-(4-{3-Fluoro-5-[1-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid methyl ester



- The procedure from Example 294, Step C is utilized with 3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester and 2-methyl-4-trifluoromethyl-benzoic acid to afford about 0.12 g (50%) of desired product.  
15  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ); MS ( $\text{ES}^+$ )  $m/z$  mass calcd for  $\text{C}_{28}\text{H}_{27}\text{F}_4\text{NO}_4$  517, found 518 ( $M + 1$ , 100%).

### Step B

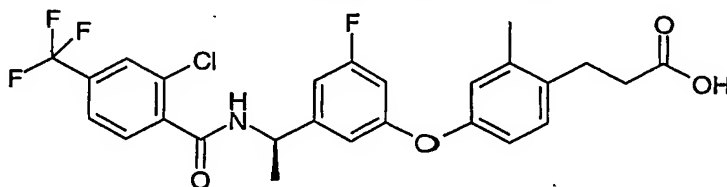
- 20 (R)-3-(4-{3-Fluoro-5-[1-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid

The procedure from Example 295 is utilized with (R)-3-(4-{3-fluoro-5-[1-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid methyl ester to afford about 0.01 g (87%) of desired product.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ); MS ( $\text{ES}^+$ )  $m/z$  mass calcd for  $\text{C}_{27}\text{H}_{25}\text{F}_4\text{NO}_4$  503, found 504 ( $M + 1$ , 100%).



Example 298

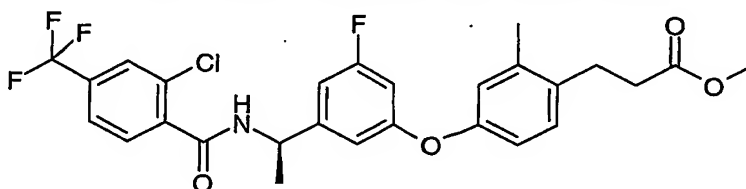
(R)-3-(4-{3-Fluoro-5-[1-(2-chloro-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid



5

Step A

(R)-3-(4-{3-Fluoro-5-[1-(2-chloro-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid methyl ester



The procedure from Example 294, Step C is utilized with 3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester and 2-chloro-4-trifluoromethyl-benzoic acid to afford about 0.13 g (54%) of desired product. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>27</sub>H<sub>24</sub>ClF<sub>4</sub>NO<sub>4</sub> 537, found 538 (M + 1, 100%).

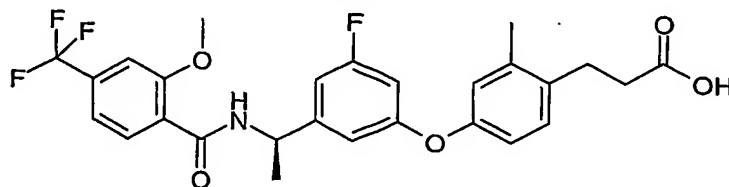
Step B

(R)-3-(4-{3-Fluoro-5-[1-(2-chloro-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid

The procedure from Example 295 is utilized with (R)-3-(4-{3-fluoro-5-[1-(2-chloro-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid methyl ester to afford about 0.01 g (84%) of desired product. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>26</sub>H<sub>22</sub>ClF<sub>4</sub>NO<sub>4</sub> 523, found 524 (M + 1, 100%).

Example 299

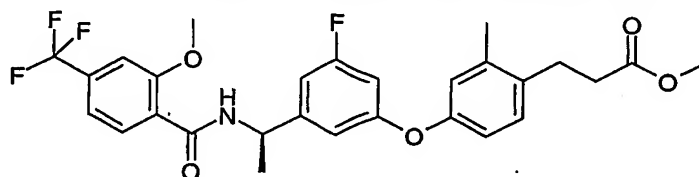
(R)-3-(4-{3-Fluoro-5-[1-(2-methoxy-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid



5

Step A

(R)-3-(4-{3-Fluoro-5-[1-(2-methoxy-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid methyl ester



The procedure from Example 294, Step C is utilized with 3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester and 2-methoxy-4-trifluoromethyl-benzoic acid to afford about 0.12 g (51%) of desired product. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>28</sub>H<sub>27</sub>F<sub>4</sub>NO<sub>5</sub> 533, found 534 (M + 1, 100%).

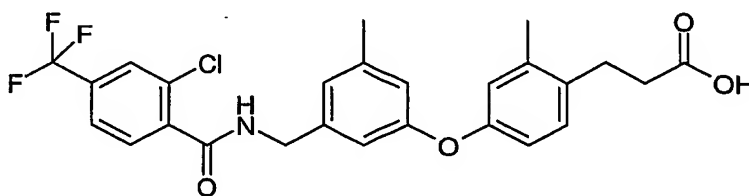
Step B

(R)-3-(4-{3-Fluoro-5-[1-(2-methoxy-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid

The procedure from Example 295 is utilized with (R)-3-(4-{3-fluoro-5-[1-(2-methoxy-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid methyl ester to afford about 0.11 g (94%) of desired product. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>27</sub>H<sub>25</sub>F<sub>4</sub>NO<sub>5</sub> 519, found 520 (M + 1, 100%).

Example 300

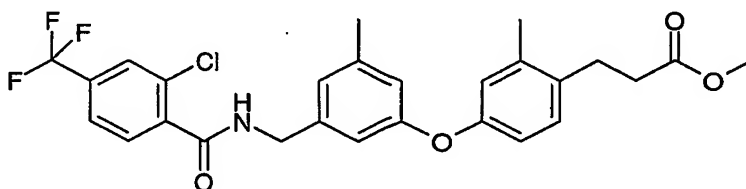
3-(4-{3-[(2-Chloro-4-trifluoromethyl-benzoylamino)-methyl]-5-methyl-phenoxy}-2-methyl-phenyl)-propionic acid



5

Step A

3-(4-{3-[(2-Chloro-4-trifluoromethyl-benzoylamino)-methyl]-5-methyl-phenoxy}-2-methyl-phenyl)-propionic acid methyl ester



The procedure from Example 294, Step C is utilized with 3-[4-(3-aminomethyl-5-methyl-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester and 2-chloro-4-trifluoromethyl-benzoic acid to afford about 0.23 g (42%) of desired product.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ); MS ( $\text{ES}^+$ )  $m/z$  mass calcd for  $\text{C}_{27}\text{H}_{25}\text{ClF}_3\text{NO}_4$  519, found 520 ( $\text{M} + 1$ , 100%).

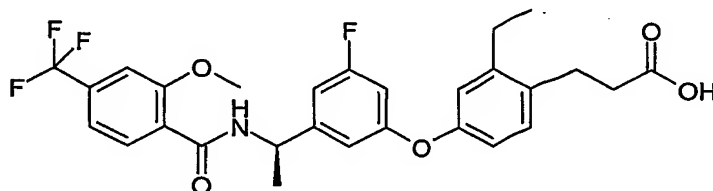
Step B

3-(4-{3-[(2-Chloro-4-trifluoromethyl-benzoylamino)-methyl]-5-methyl-phenoxy}-2-methyl-phenyl)-propionic acid

The procedure from Example 295 is utilized with 3-(4-{3-[(2-chloro-4-trifluoromethyl-benzoylamino)-methyl]-5-methyl-phenoxy}-2-methyl-phenyl)-propionic acid methyl ester to afford about 0.2 g (93%) of desired product.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ); MS ( $\text{ES}^+$ )  $m/z$  mass calcd for  $\text{C}_{26}\text{H}_{23}\text{ClF}_3\text{NO}_4$  505, found 506 ( $\text{M} + 1$ , 100%).

Example 301

3-(2-Ethyl-4-{3-fluoro-5-[1-(2-methoxy-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenyl)-propionic acid

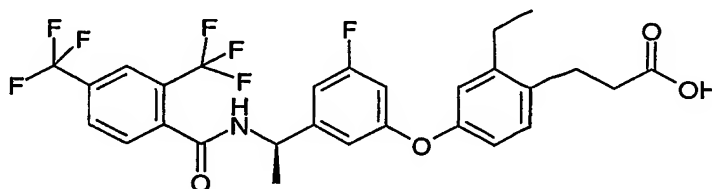


5 The title compound is prepared according to Example 2 by using 2-methoxy-4-trifluoromethyl-benzoic acid and 3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester to afford about 143 mg (81%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>28</sub>H<sub>27</sub>O<sub>5</sub>NF<sub>4</sub> 533, found 534 (M + 1, 100%).

10

Example 302

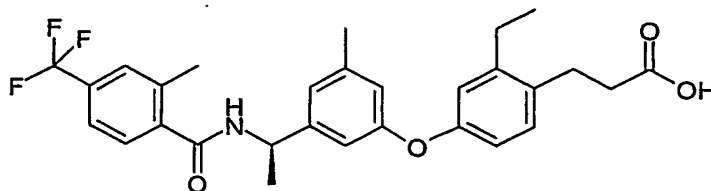
3-(4-{3-[1-(2,4-Bis-trifluoromethyl-benzoylamino)-ethyl]-5-fluoro-phenoxy}-2-ethyl-phenyl)-propionic acid



15 The title compound is prepared according to Example 2 by using 2,4-bis-trifluoromethyl-benzoic acid and 3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester to afford about 38 mg (90%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>28</sub>H<sub>24</sub>O<sub>4</sub>NF<sub>7</sub> 571, found 572 (M + 1, 100%).

Example 303

3-(2-Ethyl-4-{3-methyl-5-[1-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenyl)-propionic acid

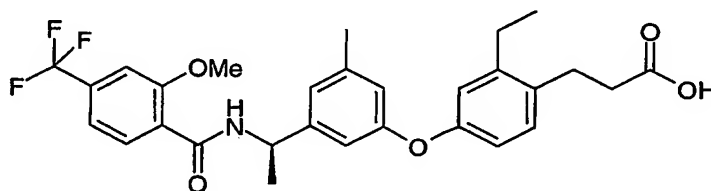


5 The title compound is prepared according to Example 131 by using 2-methyl-4-trifluoromethyl-benzoic acid and 3-{4-[3-(1-amino-ethyl)-5-methyl-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester to afford about 83 mg (70%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>29</sub>H<sub>30</sub>O<sub>4</sub>NF<sub>3</sub> 513, found 514 (M + 1, 100%).

10

Example 304

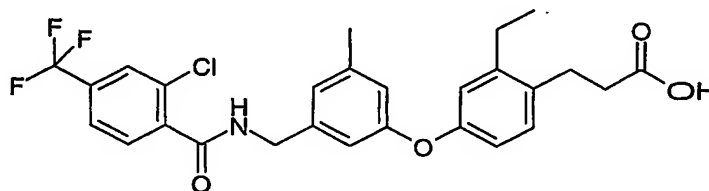
3-(2-Ethyl-4-{3-[1-(2-methoxy-4-trifluoromethyl-benzoylamino)-ethyl]-5-methyl-phenoxy}-phenyl)-propionic acid



15 The title compound is prepared according to Example 131 by using 2-methoxy-4-trifluoromethyl-benzoic acid and 3-{4-[3-(1-amino-ethyl)-5-methyl-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester to afford about 232 mg (82%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>29</sub>H<sub>30</sub>O<sub>5</sub>NF<sub>3</sub> 529, found 530 (M + 1, 100%).

Example 305

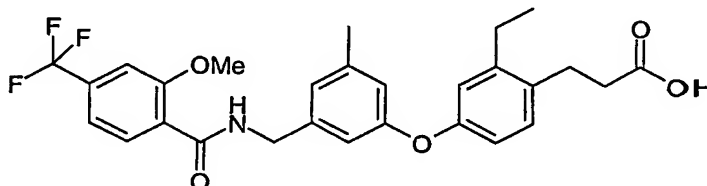
3-(4-{3-[(2-Chloro-4-trifluoromethyl-benzoylamino)-methyl]-5-methyl-phenoxy}-2-ethyl-phenyl)-propionic acid



The title compound is prepared according to Example 132 by using 2-chloro-4-trifluoromethyl-benzoic acid and 3-[4-(3-aminomethyl-5-methyl-phenoxy)-2-ethyl-phenyl]-propionic acid ethyl ester to afford about 217 mg (60%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>27</sub>H<sub>25</sub>O<sub>4</sub>NF<sub>3</sub>Cl 519, found 520 and 522 (M + 1 and M + 3, 100%).

Example 306

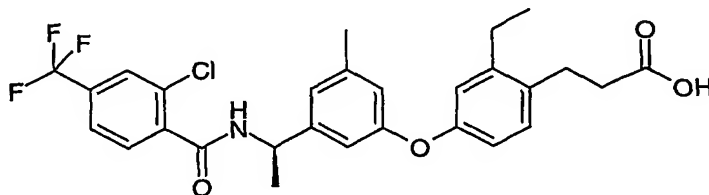
3-(2-Ethyl-4-{3-[(2-methoxy-4-trifluoromethyl-benzoylamino)-methyl]-5-methyl-phenoxy}-phenyl)-propionic acid



The title compound is prepared according to Example 132 by using 2-methoxy-4-trifluoromethyl-benzoic acid and 3-[4-(3-aminomethyl-5-methyl-phenoxy)-2-ethyl-phenyl]-propionic acid ethyl ester to afford about 115 mg (79%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>28</sub>H<sub>28</sub>O<sub>5</sub>NF<sub>3</sub> 515, found 516 (M + 1, 100%).

Example 307

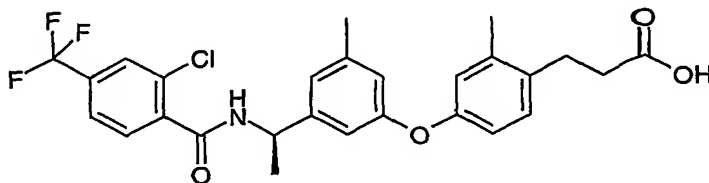
3-(4-{3-[1-(2-Chloro-4-trifluoromethyl-benzoylamino)-ethyl]-5-methyl-phenoxy}-2-ethyl-phenyl)-propionic acid



The title compound is prepared according to Example 131 by using 2-chloro-4-trifluoromethyl-benzoic acid and 3-{4-[3-(1-amino-ethyl)-5-methyl-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester to afford about 67 mg (33%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>28</sub>H<sub>27</sub>O<sub>4</sub>NF<sub>3</sub>Cl 533, found 534 and 536 (M + 1 and M + 3, 100%).

Example 308

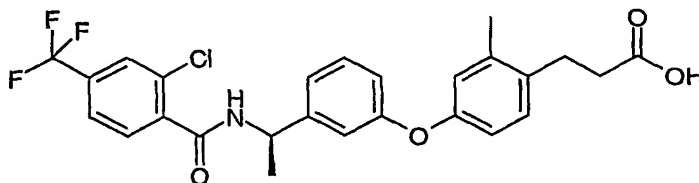
3-(4-{3-[1-(2-Chloro-4-trifluoromethyl-benzoylamino)-ethyl]-5-methyl-phenoxy}-2-methyl-phenyl)-propionic acid



The title compound is prepared according to Example 124 by using 2-chloro-4-trifluoromethyl-benzoic acid and 3-{4-[3-(1-amino-ethyl)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester to afford about 132 mg (80%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>27</sub>H<sub>25</sub>O<sub>4</sub>NF<sub>3</sub>Cl 519, found 520 and 522 (M + 1 and M + 3, 100%).

Example 309

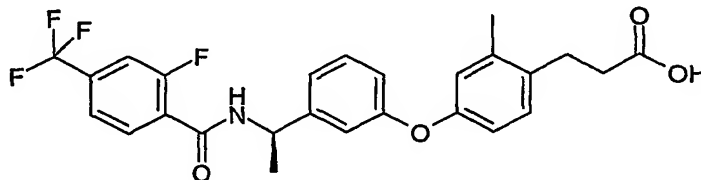
3-(4-{3-[1-(2-Chloro-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid



The title compound is prepared according to Example 100 by using 2-chloro-4-trifluoromethyl-benzoic acid and 3-{4-[3-(1-amino-ethyl)-phenoxy]-2-methyl-phenyl}-propionic acid methyl ester to afford about 638 mg (69%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>26</sub>H<sub>23</sub>O<sub>4</sub>NF<sub>3</sub>Cl 505, found 506 and 508 (M + 1 and M + 3, 100%).

Example 310

3-(4-{3-[1-(2-Fluoro-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid

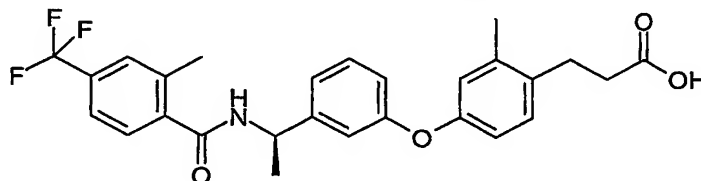


The title compound is prepared according to Example 100 by using 2-fluoro-4-trifluoromethyl-benzoic acid and 3-(4-{3-[1-(2-fluoro-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid to afford about 662 mg (74%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>26</sub>H<sub>23</sub>O<sub>4</sub>NF<sub>4</sub> 489, found 490 (M + 1, 100%).



Example 311

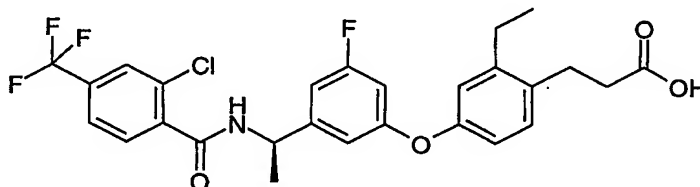
3-(2-Methyl-4-{3-[1-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenyl)-propionic acid



The title compound is prepared according to Example 100 by using 2-methyl-4-trifluoromethyl-benzoic acid and 3-(4-{3-[1-(2-fluoro-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-methyl-phenyl)-propionic acid to afford about 486 mg (55%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ); MS ( $\text{ES}^+$ )  $m/z$  mass calcd for  $\text{C}_{27}\text{H}_{26}\text{O}_4\text{NF}_3$  485, found 486 ( $\text{M} + 1$ , 100%).

Example 312

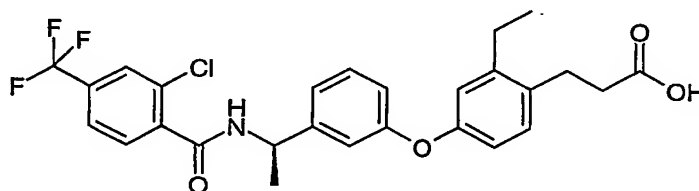
3-(4-{3-[1-(2-Chloro-4-trifluoromethyl-benzoylamino)-ethyl]-5-fluoro-phenoxy}-2-ethyl-phenyl)-propionic acid



The title compound is prepared according to Example 2 by using 2-chloro-4-trifluoromethyl-benzoic acid and 3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester to afford about 166 mg (28%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ); MS ( $\text{ES}^+$ )  $m/z$  mass calcd for  $\text{C}_{27}\text{H}_{24}\text{O}_4\text{NE}_4\text{Cl}$  537, found 538 and 540 ( $\text{M} + 1$  and  $\text{M} + 3$ , 100%).

Example 313

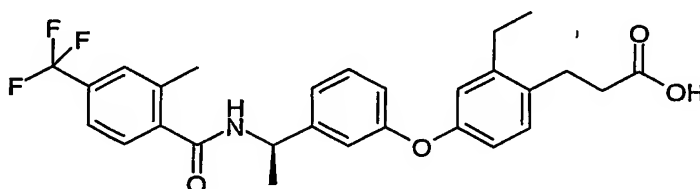
3-(4-{3-[1-(2-Chloro-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-2-ethyl-phenyl)-propionic acid



The title compound is prepared according to Example 296 by using 2-chloro-4-trifluoromethyl-benzoic acid and 3-{4-[3-(1-amino-ethyl)-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester to afford about 456 mg (86%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>27</sub>H<sub>25</sub>O<sub>4</sub>NF<sub>3</sub>Cl 519, found 520 and 522 (M + 1 and M + 3, 100%).

Example 314

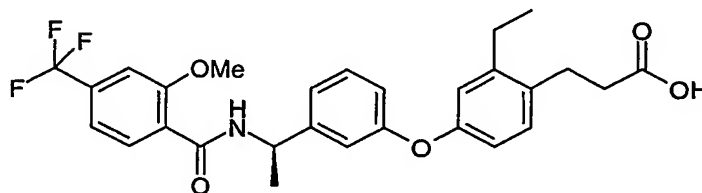
3-(2-Ethyl-4-{3-[1-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenyl)-propionic acid



The title compound is prepared according to Example 296 by using 2-methyl-4-trifluoromethyl-benzoic acid and 3-{4-[3-(1-amino-ethyl)-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester to afford about 401 mg (79%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>28</sub>H<sub>28</sub>O<sub>4</sub>NF<sub>3</sub> 499, found 500 (M + 1, 100%).

Example 315

3-(2-Ethyl-4-{3-[1-(2-methoxy-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenyl)-propionic acid

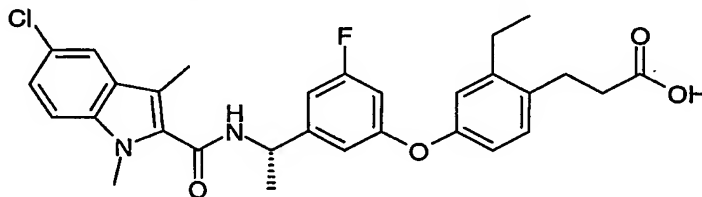


5 The title compound is prepared according to Example 296 by using 2-methyl-4-trifluoromethyl-benzoic acid and 3-{4-[3-(1-amino-ethyl)-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester to afford about 450 mg (86%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>28</sub>H<sub>28</sub>O<sub>5</sub>NF<sub>3</sub> 515, found 516 (M + 1, 100%).

10

Example 316

3-[4-(3-{1-[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-fluorophenoxy)-2-ethyl-phenyl]-propionic acid

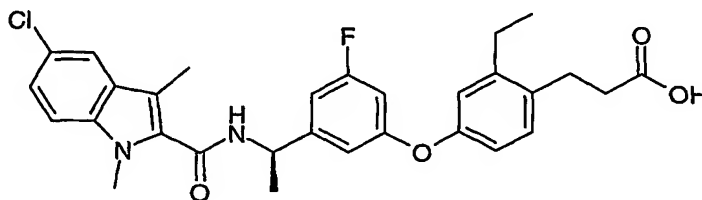


15 The title compound is prepared according to Example 2 by using 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid and 3-{4-[3-(1-amino-ethyl)-5-fluorophenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester to afford about 76 mg (100%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>30</sub>H<sub>30</sub>O<sub>4</sub>N<sub>2</sub>FCI 536, found 537 and 539 (M + 1 and M + 3, 100%).

20

Example 317

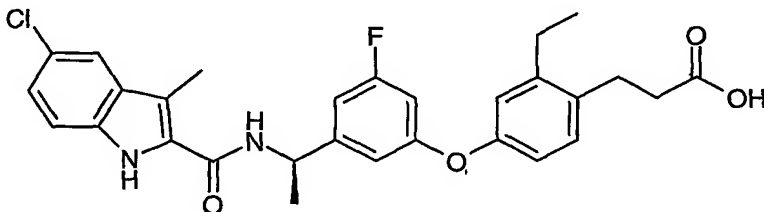
3-[4-(3-{1-[(5-Chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-fluoro-phenoxy)-2-ethyl-phenyl]-propionic acid



The title compound is prepared according to Example 2 by using 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid and 3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester to afford 2.48 g (45%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>30</sub>H<sub>30</sub>O<sub>4</sub>N<sub>2</sub>FCI 536, found 537 and 539 (M + 1 and M + 3, 100%).

Example 318

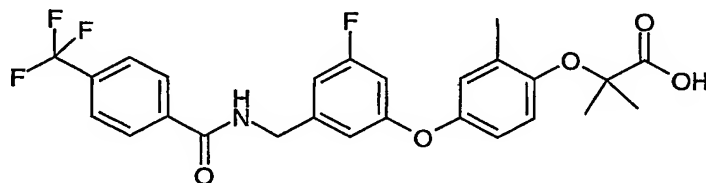
3-[4-(3-{1-[(5-Chloro-3-methyl-1H-indole-2-carbonyl)-amino]-ethyl}-5-fluoro-phenoxy)-2-ethyl-phenyl]-propionic acid



The title compound is prepared according to Example 2 by using 5-chloro-3-methyl-1H-indole-2-carboxylic acid and 3-{4-[3-(1-amino-ethyl)-5-fluoro-phenoxy]-2-ethyl-phenyl}-propionic acid ethyl ester to afford about 240 mg (40%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>29</sub>H<sub>28</sub>O<sub>4</sub>N<sub>2</sub>FCI 522, found 523 and 525 (M + 1 and M + 3, 100%).

Example 319

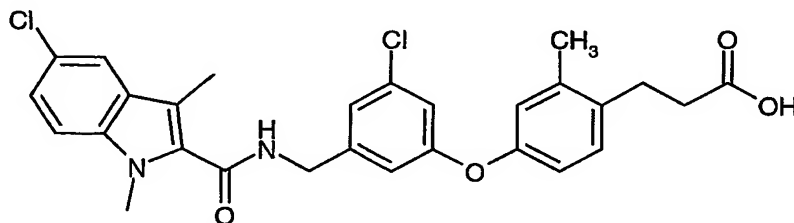
2-(4-{3-Fluoro-5-[(4-trifluoromethyl-benzoylamino)-methyl]-phenoxy}-2-methyl-phenoxy)-2-methyl-propionic acid



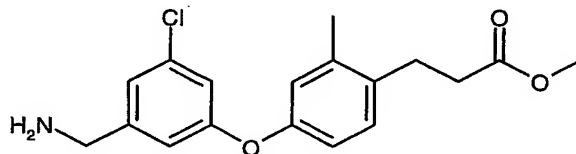
The title compound is prepared according to Example 48 by using 4-trifluoromethyl-benzoic acid and 2-[4-(3-aminomethyl-5-fluoro-phenoxy)-2-methyl-phenoxy]-2-methyl-propionic acid ethyl ester to afford about 111 mg (93%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>26</sub>H<sub>23</sub>O<sub>5</sub>NF<sub>4</sub> 505, found 506 (M + 1, 100%).

Example 320

3-[4-(3-Chloro-5-[(5-chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl)-phenoxy]-2-methyl-phenyl]-propionic acid

Preparation of Intermediate

3-[4-(3-Aminomethyl-5-chloro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester

Step A

3-[4-(3-Chloro-5-cyano-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester

The compounds of 3-chloro-5-fluoro-benzonitrile (2.0 g, 134.9 mmol), 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (2.7 g, 13.5 mmol) (*J.Chem.Soc.Perkin Trans.1*; 4; 1990; 1041-1045) and cesium carbonate (8.4 g, 25.7

mmol) are added to dimethylformamide (20 ml) and heated overnight at 85 °C under nitrogen. After cooling, water is added and extracted 3 times with ethyl acetate, washed with brine, dried over sodium sulfate and concentrated under reduced pressure.

Purification by flash chromatography, eluting with 10 % EtOAc in hexane then 15 %

- 5 EtOAc in hexane provides the title compound (2.8 g, 65 %). MS(ES<sup>+</sup>): 347 (M+NH<sub>4</sub><sup>+</sup>); <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>).

#### Step B

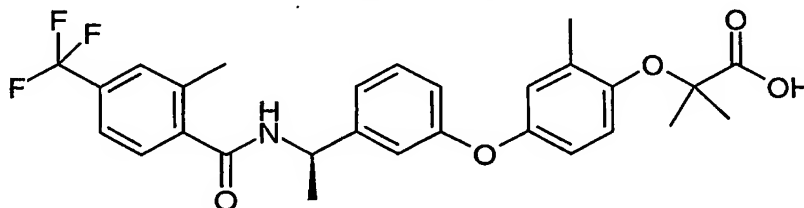
3-[4-(3-Aminomethyl-5-chloro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester

- Compound obtained from Step A (208.0. mg, 0.7 mmol) is reacted with  
 10 platinum oxide (41.0 mg) in methanol (100 mL) and acetic acid (0.5 mL) at room temperature with 60 psi hydrogen for about 3 hours in a Parr shaker. Reaction mixture is filtered and concentrated under reduced pressure with rt bath. Purification by SCX column, eluting with 10 % ammonia (2.0 M in methanol) in dichloromethane affords the title compound (81.0 mg, 38%) that is utilized without purification. MS(ES<sup>+</sup>): 334  
 15 (M+H<sup>+</sup>); <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>).

- The final compound of 3-[4-(3-chloro-5-[(5-chloro-1,3-dimethyl-1H-indole-2-carbonyl)-amino]-methyl)-phenoxy)-2-methyl-phenyl]-propionic acid is prepared according to Example 1 utilizing 5-chloro-1,3-dimethyl-1H-indole-2-carboxylic acid (Intermediate 4) and 3-[4-(3-aminomethyl-5-chloro-phenoxy)-2-methyl-phenyl]-propionic acid methyl ester. Exact mass calcd for C<sub>28</sub>H<sub>26</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>4</sub> (M+H<sup>+</sup>): 525.1348, found 525.1332; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

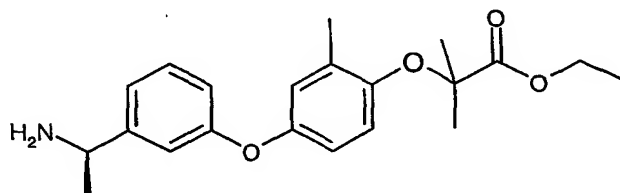
#### Example 321

- 2-Methyl-2-(2-methyl-4-{3-[1-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenoxy)-propionic acid



Preparation of intermediate

2-{4-[3-(1-amino-ethyl)-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl ester

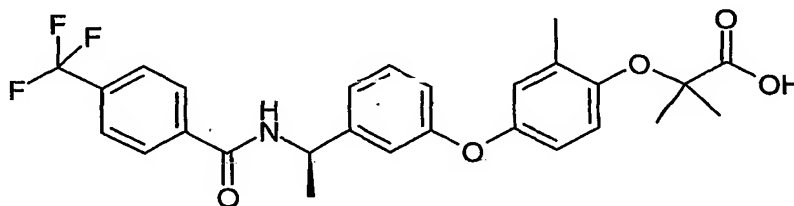


5 2-{4-[3-(1-Tert-butoxycarbonylamino-ethyl)-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl ester (0.5 g, 21.9 mmol) is dissolved in 4M HCl in dioxane (80 mL) with an ice bath in place. Bath is removed in 20 minutes and the reaction is stirred for about 1 hour. The reaction is concentrated under reduced pressure which provides the HCl salt of the title compound (0.42 g, 92%). MS(ES<sup>+</sup>): 376 (M+H<sup>+</sup>); <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>).

10 The title compound of 2-methyl-2-(2-methyl-4-{3-[1-(2-methyl-4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenoxy)-propionic acid is prepared according to Example 1 by using 4-trifluoromethyl-benzoic acid (Example 10) and 2-{4-[3-(1-amino-ethyl)-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl ester. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>28</sub>H<sub>28</sub>F<sub>3</sub>N O<sub>5</sub> 516.1998, found 516.1987 (M + 1, 100%).

Example 322

2-Methyl-2-(2-methyl-4-{3-[1-(4-trifluoromethyl-benzoylamino)-ethyl]-phenoxy}-phenoxy)-propionic acid



20 The title compound is prepared according to Example 321 by using 4-trifluoromethyl-benzoic acid and 2-{4-[3-(1-amino-ethyl)-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid ethyl ester to afford about 48 mg (64%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>); MS (ES<sup>+</sup>) *m/z* mass calcd for C<sub>27</sub>H<sub>26</sub>O<sub>5</sub>NF<sub>3</sub> 501, found 502 (M + 1, 100%).